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Examining the predictive accuracy of metabolomics for small for gestational age babies: a systematic review

| Journal: | BMJ Open |
|-------------------------------|---|
| Manuscript ID | bmjopen-2019-031238 |
| Article Type: | Research |
| Date Submitted by the Author: | 23-Apr-2019 |
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| Keywords: | small for gestational age, fetal growth restriction, metabolomics, gas- chromatography, mass spectrometry |

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| 3 4 5 | 1 | RESEARCH ARTICLE: SYSTEMATIC REVIEW |
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| 6 7 | 2 | Examining the predictive accuracy of metabolomics for small for gestational |
| 8 9 10 | 3 | age babies: a systematic review |
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| 9 | |
| 10 | Word Count: |
| 11 | Abstract: 296 words |
| 12 | Main text 4,106 words |
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1 ABSTRACT

2 **Introduction:** To date, there is no robust enough test to predict small for gestational

3 age (SGA) infants, which are at increased life-long risk of morbidity and mortality.

4 **Objective**: To determine the accuracy of metabolomics in predicting SGA babies and

5 elucidate which metabolites were found to be predictive of this condition.

Data sources: Two independent researchers explored 11 electronic databases and
grey literature in February 2018 and November 2018, covering publications from
1998 to 2018. Both researchers performed data extraction and quality assessment
independently. Discrepancies were resolved by a third researcher.

Study eligibility criteria: Cohort or nested case-control studies were included, which
investigated pregnant women and performed metabolomics analysis to evaluate SGA
infants. The primary outcome was birthweight <10th centile - as a surrogate for fetal
growth restriction - by population-based or customized charts.

Study appraisal and synthesis methods: Data on study design, obstetric variables and sampling, metabolomics technique, chemical class of metabolites, and prediction accuracy measures were extracted by two independent researchers. Authors were contacted to provide additional data when necessary.

Results: A total of 9,181 references were retrieved. Of these, 273 were duplicate, 18 19 8,760 were removed by title or abstract, and 133 were excluded by full text content. Thus, 15 studies were included. Only two studies used the 5th centile as a cutoff, and 20 most reports sampled 2nd trimester pregnant women. Liquid-chromatography coupled 21 22 to mass spectrometry was the most common metabolomics approach. Untargeted studies in the 2nd trimester provided the largest number of predictive metabolites, 23 using maternal blood or hair. Fatty acids, phosphosphingolipids, and amino acids 24 25 were the most prevalent predictive chemical subclasses.

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Conclusions and Implications: Significant heterogeneity participant of characteristics and methods employed among studies precluded a meta-analysis. Compounds related to lipid metabolism should be validated up to the 2nd trimester in different settings. Systematic review registration number: CRD42018089985. **Keywords**: small for gestational age, fetal growth restriction, metabolomics, prediction, gas-chromatography, mass spectrometry, vitamin D, homocysteine, lipids, fatty acids. STRENGHTS AND LIMITATIONS OF THIS STUDY

- To our knowledge, this is the first systematic review to assess the predictive accuracy of metabolomics for an adverse pregnancy outcome.
- Using SGA as surrogate for fetal growth restriction just as in epidemiological investigations – improves the translational potential of metabolomics.
- Identification of techniques, types of maternal samples and chemical classes paves the way for future metabolomics investigations on fetal growth patterns.
- Available data could not support a meta-analysis; further studies should
 - include accuracy measures of individual metabolites or chemical subclasses in predicting SGA.

 ORIGINAL PROTOCOL: Leite DFB, Morillon A-C, Melo Júnior EF, *et al.*Metabolomics for predicting fetal growth restriction: protocol for a systematic review
and meta-analysis. *BMJ Open* 2018;8:e022743. doi:10.1136/bmjopen-2018-022743.

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1 INTRODUCTION

Fetal growth restriction (FGR) and small for gestational age (SGA) infants are major concerns in modern obstetrics. [1–3] SGA is commonly used as a proxy for FGR, [4] despite the subtle differences between these two pathological conditions. The prevalence of both varies according to criteria applied and on the population and setting, although it reaches as much as 25% in low and middle-income countries. [5] SGA newborns may have adverse health effects, such as stillbirth, [4] perinatal asphyxia, [6] impaired neurodevelopment, [7] and increased cardiovascular risk. [8,9] To date, there are no robust prediction tools for SGA using clinical factors, [10,11] ultrasound data, [12,13] or placental biomarkers. [14]

For hypothesis generating or validation purposes, metabolomics is a novel area of biomarker, discovery, development and clinical diagnostics in translational medicine. [15,16] Metabolomics is the study of all metabolites [15,16] in a given sample, i.e. low molecular weight compounds (50-2000 Da) that are intermediates of biochemical reactions and metabolic pathways, considered to directly reflect cellular activity and phenotype. [15,16] Recent studies have evaluated the pathophysiology [17-20] of SGA with metabolomics. However, little is known about the potential of metabolomics to identify predictive compounds of SGA.

Since metabolomics can identify multiple metabolites from low volume
samples, and create a model from a collection of these samples, [15] it is a promising
technology for hypothesis generation in a heterogeneous condition such as SGA.
The prediction of SGA in pregnancy would help refer women to specialized care
facilities, improving maternal and neonatal outcomes. [21,22]

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In this context, the main objective of this systematic review was to assess the
 accuracy of metabolomics techniques in predicting SGA. As a secondary aim, we
 intended to determine which metabolites are predictive of this condition.

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5 METHODS

The protocol for this systematic review was published previously. [23] This study follows international guidelines for transparency (PROSPERO, CRD 42018089985) and respects the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement. [24] This systematic review was conducted without any public involvement, and ethical approval was unnecessary.

12 Literature Search Strategy

Two independent researchers (DFBL and ACM) assessed 11 electronic databases (PubMed, EMBASE, Latin American and Caribbean Health Sciences Literature (LILACS), Scientific Electronic Library Online (Scielo), Health Technology Assessment (HTA), Database of Abstracts of Reviews of Effects (DARE), Aggressive Research Intelligence Facility (ARIF), Cumulative Index of Nursing and Allied Health Literature (CINAHL), Maternity and Infant Care (MIDIRS), Scopus, and Web of Science) and grey literature. There were no limits or language constraints; the search strategy covered published documents between 1998 and 2018. Keywords 'small for gestational age', 'metabolomics', 'prediction', 'antenatal', and variations of each, were combined with Boolean operators depending on each database requirements. The full EMBASE literature search was, as follows: ('fetal growth retardation' OR 'fetal growth restriction' OR 'intrauterine growth restriction' OR 'intrauterine growth retardation' OR 'small for gestational age') AND ('metabolomic*' OR 'metabonomic*'

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OR 'metabolit* 'H NMR' OR 'proton NMR' OR 'proton nuclear magnetic resonance'
OR 'liquid chromatogra*' OR 'gas chromatogra*' OR 'UPLC' OR 'ultra-performance'
OR 'ultra performance liquid chromatograph*') AND ('pregnan*' OR 'antenat*' OR
'ante nat*' OR 'prenat*' OR 'pre nat*') AND ('screen*' OR 'predict*' OR 'metabolic
profil*').

7 Outcomes and subgroup analysis

8 The primary outcome was SGA, as a surrogate for FGR and defined as birthweight
9 <10th centile, by population-based or customized charts. Secondary outcomes were
10 birthweight ≤5th or ≤3rd centile.

11 The intended subgroup analysis comprised: type of metabolomics technique 12 applied (nuclear magnetic resonance, NMR; gas or liquid chromatography coupled 13 with mass spectrometry, GC-MS or LC-MS respectively); maternal health status 14 before pregnancy (women with *versus* without any chronic health condition); type of 15 SGA suspected during pregnancy (early *versus* late SGA); and type of pregnancy 16 (singleton *versus* multiple pregnancy).

18 Selection Criteria of Studies, Data Collection and Analysis

19 Cohort or case-control studies were included if maternal samples were collected 20 before the clinical diagnosis of SGA, if any metabolomics technique was applied, and 21 if the results of SGA were presented. Articles presenting data from the same 22 research project but analyzing distinct metabolites or showing data from different 23 countries were included. Studies were excluded (i) according to study design; (ii) if 24 they had not applied any metabolomics technique; (iii) if they were only experimental 25 studies; (iv) if it was not possible to extract data on SGA; (v) or if they presented

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duplicate data, in which case the most complete publication was included for final analysis.

Two researchers (DFBL and ACM) independently selected studies, extracted
data and discussed discrepancies. One additional reviewer (EFMJ or RTS) helped to
decide, by majority, when no consensus was reached.

6 Piloted standardized forms were applied for data extraction, including 7 pregnancy characteristics and experimental details. The Human Metabolome 8 Database (HMDB) [25] and the Kyoto Encyclopedia of Genes and Genomes [26] 9 were used for matching chemical class and metabolic pathways of each metabolite, 10 respectively.

Risk of bias and Assessment of concerns regarding applicability

Two researchers (DFBL and ACM) independently evaluated individual studies using
the QUADAS-2 tool. [27] One of the third reviewers (EFMJ, or RTS) helped in
decision-making when no consensus was achieved.

Each study was classified as high, low, or unclear risk of bias in four Domains (Patient Selection, Index Test, Reference Standard, and Flow and Timing), and as high, low, or unclear concerns regarding applicability in the first three Domains. We did not consider two signaling guestions ("Was a case-control design avoided?", "Was there an appropriate interval between the index test and reference standard?"). The nested case-control design was an inclusion criterion and maternal samples should have been collected during pregnancy, i.e. before the SGA diagnosis. Studies were considered 'low risk', for example, (i) if pregnancy or neonatal complications were not excluded in just one group of participants or data on participant selection had been provided; (ii) if methods for sample preparation and

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interpretation were standardized or metabolite threshold was defined before the experiments (for targeted analysis); (iii) if the adequacy and reasons for choosing the reference birthweight chart had been explained; or, (iv) if large for gestational age babies had been excluded from the final comparative analysis.

Data synthesis

A quantitative summary of data was performed when any predictive accuracy measures could be extracted. Authors were contacted to provide additional information, when necessary. However, only Delplancke et al [28] replied. The estimation of likelihood ratios and hierarchical summary receiver operator characteristic curve [29] were planned, as well as assessment of heterogeneity and publication bias. [30] However, due to lack of data, a meta-analysis could not be performed. Lieu

RESULTS

Literature search characteristics

The literature search for this systematic review was performed in February 2018, and re-run in November 2018. A total of 9,181 references were retrieved (Figure 1). After the removal of duplicate records (n=273), title and abstract screening, and analysis of the remaining 148 full-text articles, 15 articles were included. [17,18,38–42,28,31–37] See Supplementary Material 1 for excluded studies.

Characteristics of the included studies

The characteristics of the included studies are shown in Table 1. The prevalence of SGA ranged from 7.3% [33] to 21.5% in cohort studies. [28] There were no studies

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using a birthweight ≤3rd centile for a definition of SGA. The time interval between
initial participant enrollment and publication varied from three [17] to 54 years, [40]
although these data were unclear in 38% of the reports. [18,28,32,33,37] In nested
case-control studies, participants were matched by maternal age, [17,18,38,42]
ethnicity, [17,18,42] parity, [38] body mass index, [17,18,42] or infant gender. [18,38]

Participant characteristics varied between studies. Regarding gestational age at assessment, samples were collected in the 2nd trimester in one half of the studies. [17,18,33,35,37,39,42] In three reports, women were assessed at least twice. [34,38,41] In one study, maternal blood was drawn either in the 1st or 2nd trimester; [40] and in another three studies, only samples from the 3rd trimester were considered. [28,36,41] In the latter case, maternal hair was divided according to length, allowing evaluation of 2nd and 3rd trimester metabolites. [28] Studies considering the 5th centile as the cutoff, sampled women in the 1st trimester. [31,32] Twin pregnancy was a clear exclusion criterion in most studies. [17,18,31,33– 35,37,40-42] Pregnancy aided by assisted reproduction [18,37] or women with pre-existing conditions [17,18,35,37,42] were also excluded, although these data were incompletely reported. [28,32,36,38,39,41] When both nulliparous and multiparous women were enrolled, there was no data analysis according to parity. Half of the studies considered term deliveries exclusively, [18,28,36,38-41] and the remaining studies did not differentiate results according to gestational age at birth.

Regarding clinical risk factors for SGA, only one paper mentioned a previous history of SGA, but findings were not adjusted for this variable. [32] All studies, except one, [28] cited participant smoking status. The rate of smoking habit ranged from 2.4% [18] to 47.5%. [40] It is important to note that Gernand et al [40] analyzed samples from women recruited between 1959 and 1965, when smoking while

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pregnant was encouraged, which explains the high rate of smoking participants. The duration of smoking or any differences in birthweight (absolute measures or centiles) were not clearly stated. Although more prevalent in SGA pregnancies, results did not change with this variable control. [31,32,35,37,40] Only Gong et al [41] mentioned the suspicion of SGA in pregnancy, exhibiting decreasing abdominal circumference growth velocity between 20-36 wks. However, on final analysis, these babies were nts not su., grouped with infants not suspected during pregnancy.

| Table ' | 1. Main characteristics of | included stuc | lies | | | mjopen-2019-031238 1 by copyright, inclu | | |
|------------------------------|---|----------------------------|-------------------------------|---|--|---|----------------------------|---|
| Authors, year | Country, year of participants enrolment | Study design | Affected/ non- affected | Gestational age at assessment | Type of pregnancy | ding ₱arity for us Eug | Birthweight curve | - |
| Outcome: SGA | <5 th centile | | | | | gust 20 Enseigr ses rela | | - |
| Costet N et al, 2011 | France, 2002-2006 (PELAGIE Cohort) | Nested case- control | 134/ 399 | 11w | Single pregnancy | Nullipacts and parous worthon, unclear | Customized curve | - |
| Ertl R et al, 2012 | United Kingdom ^a | Nested case- control | 150/ 1,000 | 11 ⁺⁰ -13 ⁺⁶ w | Unclear | 55, a % B ulliparous in SGASCoup, 48.1% nulliparoius in control | Population-based charts | _ |
| Outcome: SGA | <10 th centile | | | r. | | ttp://br 3) . Ing, A | | - |
| Grandone E et al, 2006 | Italy ^a | Cohort | 31/ 393 | 17.1 ± 1.2w⁵ (mean) | Single pregnancy; no maternal pre-existing conditions | I training, a | Population-based charts | - |
| van Eijsden M et al, 2008 | Netherlands, 2003- 2004 (ABCD Study) | Cohort | 429/ 3275 | 13.5 ± 3.3w (mean) | Term deliveries, no diabetes or hypertension | ng, and similar t | Population-based charts | - |
| Horgan RP et al, 2011 | Australia, 2008-2011 (SCOPE Cohort) | Nested case- control | 40/ 40 | 14-16w | Single pregnancy; no other pregnancy complications | د Nutiparous 13 20 20 | Customized curve | - |
| Gernand AD et al, 2013 | United States, 1959- 1965 (Collaborative Perinatal Project) | Nested case- control | 395/ 1751 | ≤26w | Single pregnancy; term deliveries | Parous women Parous women A ge | Population-based charts | - |
| Sulek K et al, 2014 | Singapore ^a (GUSTO Study) | Nested case- control | 41/ 42 | 26-28w | Single pregnancy; term deliveries; no maternal pre-existing conditions | Nulliparous women, unclear proportions | Population-based charts | - |
| Choi R et al, 2016 | South Korea, 2012- 2013 | Cohort | 39/ 217 | 1 st , 2 nd or 3 rd trimester | Single pregnancies | Nulliparo wom€n, unclear | Population-based charts | - |

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| 6 7 8 9 | Kiely ME et al, 2016 | Ireland, 2008-2011 (SCOPE Cohort) | Cohort | 190/ 1578 | 14-16w | Single pregnancy; no maternal pre-existing conditions | for Nutiparous us Engu | Customized curve |
| 10 11 12 | Ong YL et al, 2016 | Singapore ^a (GUSTO Study) | Cohort | 83/ 827 | 26-28w | Single pregnancy; no maternal chronic illness | 4.5 ment to v | Population-based charts |
| 13 14 15 16 | Wang Y et al, 2016 | Taiwan, 2000-2001 (Taiwan Maternal and Infant Cohort Study) | Cohort | 35/ 188 | 3 rd trimester | Unclear; term deliveries | text 46 and dat dat dat dat dat dat dat dat dat dat | Population-based charts |
| 17 18 19 20 | Delplancke TDJ et al, 2018 | New Zealand ^a | Cohort | 20/ 73 | 34-37w | Unclear; term deliveries | ing ABB mining, | Customized curve |
| 21 22 23 | Luthra G et al, 2018 | United States, 2010- 2012 (TIDES Study) | Nested case- control | 53/ 106 | 1 st and 2 nd trimester | Single pregnancies; term deliveries | Agent States Sta | Customized curve |
| 24 25 26 27 | Gong S et al, 2018 | United Kingdom, 2008- 2012 (POP study) | Nested case- control | 162/259 | 36w | Single pregnancies; term deliveries | and simila | Customized curve |
| 28 29 30 31 32 | Morillon A-C et al, 2018 | 2008-2011 (SCOPE Study) | Nested case- control | 40/40 | 20w | Single pregnancies | Jugge 13, 2025 r technologies | Customized curve |
| 33 34 | ^a Unclear period | d of participant recruitment. | ^b Mean for | all study partici | pants. | | at | |
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1 Subgroup analysis

Due to unavailable data, the only subgroup analysis performed was related to the metabolomics approach applied (Table 2). There was no mention of adherence to metabolomics reporting data guidelines. LC-MS was the leading technique used. Three studies have investigated metabolites related to environmental exposure, from contaminated water, [31] consumer products, [36] or pesticides, [42] while others have analyzed endogenous compounds. [32-35,37-40] Only Luthra et al conducted a biomarker validation study, [38] while Gong et al [41] chose to analyze the top ten statistically different metabolites according to infant sex.

Maternal blood was the most common biological sample analyzed by LC-MS in all studies, [17,32,34–37,39–41] except for one, which used GC-MS.[39] Maternal urine was analyzed by NMR, [38] GC-MS [36] or LC-MS. [42] There was only one report using amniotic fluid [33] and two using maternal hair, [18,28] all applying GC-MS. The period of laboratory analysis was rarely specified, which made it impossible to estimate total time of sample storage.

Untargeted studies reported diverse metabolic features. Authors matched the peaks with an in-house library [18,28] or HMDB-related database. [17,42] Horgan et al [17] found 785 compounds both in maternal and newborn samples; their predictive model included 19 metabolites (only five could be putatively identified, Table 2) and used 2nd trimester maternal blood. Sulek et al [18] and Delplancke et al [28] prepared and analyzed samples with GC-MS using similar protocols. Sulek et al [18] identified 32 statistically different chromatographic features from which they built a (2predictive model using five metabolites. including two fatty acids methyloctadecanoate and margarate). In contrast, Delplancke et al, [28] identified 198 metabolites, including three fatty acids (margaric, pentadecanoic, and myristic

| Table 2. Sub | group analysis of included stud | ies according to | which metabole | BMJ Open omics technique wa | as applied. | mjopen-2019-031238 on 1 1 by copyright, including | | | Page 1 |
|----------------------------------|---|---|----------------------|--|---|--|-----------------------------|----------------------|--------|
| Authors/ year | Metabolomics Technique | Maternal sample/ Storage temperature | Prediction model* | Targeted compounds | Coefficient of variation/ Limits of quantitation | For Comparison Compari | Sensitivity/ Specificity | AUC | - |
| Nuclear mag | netic resonance | | | | | d to | | | |
| Luthra G et al, 2018 | ¹ H-NMR 1D NOESY with pre-saturation and homonuclear 2D <i>J</i> -resolved at 300 K Bruker 600 MHz Advance III HD spectrometer | Urine/ -80°C | Targeted | Tyrosine, acetate, formate, trimethylamine | NA | ownloaded from http: t Superieur (ABES) . t texpand data mining | | | - |
| Gas chromat | ography coupled to mass spe | ectrometry | | 6 | | g, Al tr | | | - |
| Costet N et al, 2011 | GC-MS Simple head space SPME- Capillary GC | Urine/ -20°C | Targeted | Trichloroacetic acid | <5%/ 0.01mg/L | ainonen. Nang, and | 0.1/ 0.93 | | - |
| Sulek K et al, 2014 | GC-MS Thermo Trace GC Ultra system coupled to ISQ mass selective detector Capillary GC column: Phenomenex ZB-1701 (30 m x 250 µm id x 0.15 µm with 5 m guard column) | Hair/ -20ºC | Untargeted | NA | NA | ↓ Lactate ↓ Levelinate ↑2-methyloctatecanate ↑Tyrosine ↓ Maggarate | | 0.998 | - |
| Delplancke TDJ et al, 2018 | GC-MS: Agilent 7890B gas chromatograph, capillary column ZB-1701 (30m x 250µm id x 0.15µm with 5m guard column) 5977 A mass spectrometer, electron impact ionisation | Hair/ -20°C | Untargeted | NA | NA | ↑ Margaric ↑ Pentadecargeic acid ↑ Myristic ac id © f Myristic ac id © f ographi ographi ue | | 0.72 0.73 0.73 | - |

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| atography coupled to mass ៖ | spectrometry | | | | includi | 7 2 | | |
| LC-MS/MS triple quadrupole Applera API 3000, TurbolonSpray ionisation | Amniotic fluid/ -80°C | Targeted | Homocysteine | Unclear | لم Homocyster †Homocyster 1,05-£عي | gM) ວ | | |
| UPLC- MS/MS Thermo Fisher LTQ Orbitrap, ESI | Plasma/ - 80ºC | Untargeted | NA | NA | Hexacosa diglyce phosphoen | ic acid, yso- line, | | 0.9 |
| HPLC- MS/MS Shimadzu Prominence HPLC system with a column Phenomenex Luna C8 3 x 50 mm; AbSciex API-5000 triple quadrupole, ESI | Serum/ -80°C | Targeted | 25(OH)D _{2;} 25(OH)D ₃ | 6.3% ^a , 6.6% ^b (D ₂); 6.5% ^a , 7.3% ^b (D ₃)/ unclear | (12.16nğ/mL 20.54fig/a ini g, an | 8.09- L) | 0.72/ 0.45 | |
| LC-MS/MS | Serum/ -20°C | Targeted | 25(OH)D _{2;} 25(OH)D ₃ | 8.2% ^a (D ₂) 5.9% ^a (D ₃)/ <1ng/mL | sime Najiar teo | | 0.39/ 0.66 | |
| HPLC- MS/MS Waters HPLC system, Applied Biosystems API- 4000 MS/MS mass spectrometer | Serum/ -20°C | Targeted | Methylmalonic acid; homocysteine | <10%ª; <10% ^b / Unclear | No logies. | 13 2025 at | | |
| UPLC- MS/MS Waters Acquity UPLS system, Waters Triple Quadrupole TQD mass spectrometer | Serum/ -80°C | Targeted | 25(OH)D ₂ ; 25(OH)D ₃ ; 3-epi-25(OH)D ₃ . | <6% ^a ; <5% ^b / 0.57ng/mL (D ₂); 0.26ng/mL (D ₃), 0,41ng/mL (epi-D ₃) | None | | | |
| - | LC-MS/MS triple quadrupole Applera API 3000, TurbolonSpray ionisation UPLC- MS/MS Thermo Fisher LTQ Orbitrap, ESI HPLC- MS/MS Shimadzu Prominence HPLC system with a column Phenomenex Luna C8 3 x 50 mm; AbSciex API-5000 triple quadrupole, ESI LC-MS/MS HPLC- MS/MS Waters HPLC system, Applied Biosystems API- 4000 MS/MS mass spectrometer UPLC- MS/MS Waters Acquity UPLS system, Waters Triple Quadrupole | triple quadrupole Applera API 3000, TurbolonSpray ionisationfluid/ -80°CUPLC- MS/MS Thermo Fisher LTQ Orbitrap, ESIPlasma/ - 80°CHPLC- MS/MS Shimadzu Prominence HPLC system with a column Phenomenex Luna C8 3 x 50 mm; AbSciex API-5000 triple quadrupole, ESISerum/ -80°CLC-MS/MS Waters HPLC system, Applied Biosystems API- 4000 MS/MS mass spectrometerSerum/ -20°CUPLC- MS/MS Waters Acquity UPLS system, Waters Triple Quadrupole TQD mass spectrometerSerum/ -80°C | LC-MS/MS triple quadrupole Applera API 3000, TurbolonSpray ionisationAmniotic fluid/-80°CTargetedUPLC- MS/MS Thermo Fisher LTQ Orbitrap, ESIPlasma/- 80°CUntargetedHPLC- MS/MS Shimadzu Prominence HPLC system with a column Phenomenex Luna C8 3 x 50 mm; AbSciex API-5000 triple quadrupole, ESISerum/-80°CTargetedLC-MS/MS Waters HPLC system, Applied Biosystems API- 4000 MS/MS mass spectrometerSerum/-20°CTargetedUPLC- MS/MS Waters Acquity UPLS system, Waters Triple QuadrupoleSerum/-80°CTargeted | atography coupled to mass spectrometry LC-MS/MS triple quadrupole Applera API 3000, TurbolonSpray ionisation Amniotic fluid/-80°C Targeted Homocysteine UPLC-MS/MS Thermo Fisher LTQ Orbitrap, ESI Plasma/- 80°C Untargeted NA HPLC-MS/MS Shimadzu Prominence HPLC system with a column Phenomenex Luna C8 3 x 50 mm; AbSciex API-5000 triple quadrupole, ESI Serum/-80°C Targeted 25(OH)D ₂ ; 25(OH)D ₃ LC-MS/MS Serum/-20°C Targeted 25(OH)D ₂ ; 25(OH)D ₃ HPLC- MS/MS shimadzu Prominence HPLC system with a column Phenomenex Luna C8 3 x 50 mm; AbSciex API-5000 triple quadrupole, ESI Serum/-20°C Targeted 25(OH)D ₂ ; 25(OH)D ₃ LC-MS/MS Serum/-20°C Targeted Methylmalonic acid; homocysteine UPLC- MS/MS spectrometer Serum/-80°C Targeted 25(OH)D ₂ ; 25(OH)D ₃ ; 3-epi-25(OH)D ₃ ; Waters Triple Quadrupole Serum/-80°C Targeted 25(OH)D ₂ ; 25(OH)D ₃ ; | atography coupled to mass spectrometry LC-MS/MS Amniotic fluid/-80°C Targeted Homocysteine Unclear LC-MS/MS triple quadrupole Applera API 3000, TurboionSpray ionisation Amniotic fluid/-80°C Targeted NA NA UPLC- MS/MS Thermo Fisher LTQ Orbitrap, ESI Plasma/ - 80°C Untargeted NA NA HPLC- MS/MS Shimadzu Prominence HPLC system with a column Phenomenex Luna C8 3 x 50 mm; AbSciex API-5000 triple quadrupole, ESI Serum/-80°C Targeted 25(OH)D2; 25(OH)D3 6.3%*, 6.6%*, C92); 6.5%*, 7.3%* (0 ₂)/ unclear LC-MS/MS Serum/-20°C Targeted 25(OH)D2; 25(OH)D3 8.2%* (0 ₂) 6.5%*, 7.3%* (0 ₃)/ unclear LC-MS/MS Serum/-20°C Targeted Methylmaionic acid; homocysteine <10%*; <10g/mL | atography coupled to mass spectrometry atography coupled to mass spectrometry atography coupled to mass spectrometry LC-MS/MS Anniotic Targeted Homocysteine Unclear 1Homocysteine API 3000, TurbolonSpray ionisation Plasma/ - Untargeted NA NA Hexacosation UPLC-MS/MS Plasma/ - Untargeted NA NA Hexacosation UPLC-MS/MS Plasma/ - Untargeted NA NA Hexacosation HPLC-MS/MS Serum/ -80°C Targeted 25(OH)D2, 25(OH)D3 6.3%*, 7.3%* (D2) (12.16hg/m HPLC-MS/MS Serum/ -80°C Targeted 25(OH)D2, 25(OH)D3 6.3%*, 7.3%* (D2) (25.6Hg/f AbScicz API-5000 triple quadrupole, ESI Serum/ -20°C Targeted 25(OH)D2, 25(OH)D3 8.2%* (D2) Na HPLC-MS/MS Serum/ -20°C Targeted 26(OH)D2, 25(OH)D3 8.2%* (D2) Na HPLC-MS/MS Serum/ -20°C Targeted 25(OH)D2, 25(OH)D3 8.2%* (D2) Na HPLC-MS/MS Serum/ -80°C Targeted 25(OH)D2, 25(OH)D3 6.5%*, <5%*/ | atography coupled to mass spectrometry atography coupled to mass spectrometry atography coupled to mass spectrometry LC-MS/MS Amniotic fluid'-80°C Targeted Homocysteine Unclear †Homocyst@##;1,29µM; 1.05 #@BBW) UPLC-MS/MS fluid'-80°C Targeted NA NA Hexacosaf#@BW UPLC-MS/MS Plasma/- Orbitrap, ESI Untargeted NA NA Hexacosaf#@BW HPLC-MS/MS Serum/-80°C Targeted 25(OH)D_2; 25(OH)D_3 6.69% (D_2); 6.69% (D_2); 0.05% (D_3)/ | atography coupled to mass spectrometry LC-MS/MS triple quadrupole Applera API 3000. TurbolonSpray ionisation Amniotic fluid/-80°C Targeted Homocysteine Unclear [Homocystelite#1,29µM; 1,05-##1800] UPLC-MS/MS Thermo Fisher LTQ Orbitrap, ESI Plasma/- 80°C Untargeted NA NA HexacosaM#Bic acid, diglyce8bd 2yso- portspringaning/Employee HPLC-MS/MS Shimadzu Prominence HPLC system quadrupole, ESI Serum/-80°C Targeted 25(OH)D2, 25(OH)D3 6.3%*, 6.6%* (D2) 125(OH)Z1 (12.16ng/m128.09- 100 mit) 0.72/ 0.45 LC-MS/MS Shimadzu Prominence HPLC system Quadrupole, ESI Serum/-20°C Targeted 25(OH)D2, 25(OH)D3 8.2%* (D2) (12.16ng/m128.09- 100 mit) 0.39/ 0.66 LC-MS/MS Summic Serum/-20°C Targeted 25(OH)D2, 25(OH)D3 8.2%* (D2) (10.200 Name Summeter Name Summeter 0.39/ 0.66 HPLC-MS/MS System, Applied Biosystems API- 4000 MS/MS mass spectrometer Serum/-20°C Targeted 25(OH)D2, 25(OH)D3 8.2%* (D2) (D3) Name Summeter Name Summeter UPLC-MS/MS Waters Triple Quadrupole TQD mass spectrometer Serum/-80°C Targeted 25(OH)D3, 0-26/(D1); 0-26/(D1 |

| Ong YL et al, 2016 | LC-MS/MS Applied Biosystems ThermoHypersil BDS C8 reverse-phase column | Plasma/ Unclear | Targeted | 25(OH)D _{2;} 25(OH)D ₃ | ≤10,3% ^{a,b} / <1,6ng/mL | mjopen-2019-031238 on 10 9 by copyright, inguding fo | / 0.87 |
|--|--|---|--|---|--|---|--|
| Wang Y et al, 2016 | LC-MS Agilent HPLC system, Applied Biosystems Sciex API-4000 triple quadrupole mass spectrometer | Serum/ Unclear | Targeted | PFOA; long- chain PFCA | 0,83- 7,94%ª; 1,57- 24,7% ^b / 0,07- 0,45ng/mL ^e | ×č⊃ | |
| Gong S et al, 2018 | LC-MS/MS Shimadzu UK Limited UPLC system, ACE Excel 2 C18- PFP LC-column; Thermo Fisher Scientific Exactive orbitrap mass spectrometer | Serum/ Unclear | Untargeted | NA | | ¢adebinine ^f ↑N trandebinine ^f diacetygeta from http:/// diacetygeta mining, · | |
| Morillon A-C et al, 2018 | UPLC- MS/MS Waters Acquity UPLS system, Waters Synapt G2-S mass spectrometer | Urine/-80oC | Untargeted | NA | ien. | Algneining, and | |
| Others | | | | | | | |
| van Eijsden M et al, 2008 | GC-FID Solid phase extraction SPE, Capillary GC | Plasma/ - 80ºC | Semi- targeted, Lipid extraction | Elaidic, linoleic, alfa-linolenic, eicosatetraenoic, EPA, DPA, DHA DGLA, AA, Adrenic, and Osbond acids | | ↓ Eicosate∯ae (OR 1,5; 95% CI 1,07- 291), ↓DPA (OR 4,43995% CI 1,00-2,9) | |
| certain based cervonyl carr pencosenoic hydroxybutyra phosphocoline (3s)-3,4-Di-N-H | I on chromatographic peak and r nitine and/or 1-alpha,25-dihyd acid or cyclohexyl acetate or ate or hydroxy-methylpropanoat e or ubiquinone-8; acetylleucil-le hexanoyloxybutyl-1-phosphocoli | mass: Phenylac droxy-18-oxocho or octanoic acid te or methyl me leucil-norleucinal line or N-(3-h carnitine; pregar | cetylglutamine c blecalciferol; (1 d or methyl-he ethoxyacetate; l l or oleoylglycer hydroxy-propyl) inediol-3-glucuro | or formyl-N-acetyl-5- 15Z)-tetracosenoic eptenoic acid or 4 lysophosphocoline erone phosphate or arachidonoyl an | 5-methroxykynu acid or 10,1 4-hydroxy-2-oc and phosphod LPA(0:0/18:2(mine or N-m 1,20-alpha-dihyd | segments. ^d And more 14 metabolites t nurenamine; leucy deucyl-norleucine or 13-dimethyl-11-decosyne-10,13-diol c ctenal or DL-2-aninooctanoic acid c ocoline (more that 10 hits); phosphoc (9Z,12Z)) or 1-16 IlysoPE or phospho methyl N-(2-hydroxy-ethyl) arachido ydroxy-5-beta-precinane-3-glucuronide; | r sphingosine 1-phosphate or trans-selacholeic acid or 3-amino-octanoic acid coline (more than 20 hits) pcoline(O-11:1(10E)/2:0) c pnoyl amine or similar |

 19 of 55 (4OH,8Z,t18:1) sphingosine or 15-methyl-15-prostaglandin D2 or 15-R-prostaglandin E2 methylester. *Values for all statices AUC: area under the receiver operating characteristic curve: ¹H-NMR: hydrogen nuclear magnetic resonance: NOESY: nuclear Overhauser effect spectroscopy: GC-MS: gas

AUC: area under the receiver operating characteristic curve; ¹H-NMR: hydrogen nuclear magnetic resonance; NOESY: nuclear magnetic resonace; NOESY: nuclear magnetic resonance; NOESY: nuclear chromatography coupled to mass spectrometry; SPME: solid phase micro extraction; LC-MS: liquid chromatography coupled to mass spectrometry; UPLC: ultra-performance liquid chromatography; ESI: Electrospray ionisation; FID: flame ionisation detection; PFOA: perfluorooctanoic acid; PFCA: perfluorocarboxylic acid; PFDeA: perfluorodecanoic acid; PFUnDA: perfluoroundecanoic acid; EPA: eicoisapentaenoic acid; DPA: docosapentaenoic acid; DHA: docosahexa acid; DGLA: dihomo-gama-linolenic acid; AA: just 2019. Downloaded from http://bmjopen.bmj.com/ on June 13, 2025 at Agence Bibliographique nseignement Superieur (ABES) . es related to text and data mining, Al training, and similar technologies. arachidonic acid; OR: odds ratio; CI: confidence interval; NA: not applicable.

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1 Analysis of identified metabolites

The identified compounds refer to eleven HMDB chemical classes. Fatty acids
[18,28,39] comprised the most prevalent chemical class, followed by amino acids
[18,33] and phosphosphingolipids [17] (Table 3).

A total of 5,974 women were assessed for vitamin D status. Results were presented as total vitamin D, [32,35,37,40] although vitamin D₂ D₃ or 3-epi-25(OH)D₃ [35] metabolites were measured. Results were stratified according to season of maternal sampling or latitude. Either <15ng/mL (<37.5nmol/L) [40] or <20ng/mL (<50nmol/L) [32,35,37] levels characterized vitamin D deficiency, but were statistically different in SGA pregnancies only in the 1st trimester. [32] Horgan et al found a metabolite that could represent a vitamin D derivative, but it was only predictive in combination with 18 other compounds; this model had an area under the curve (AUC) of 0.90 (optimal odds ratio (OR), 44; 95%CI 9-214). [17]

The second most frequent targeted metabolite was homocysteine, [33,34] although levels were only differentiated between normal and SGA pregnancies when measured in 2nd trimester amniotic fluid, with a multiple linear regression model r^2 =0.012 and p=0.029. [33] Comparatively, the only common metabolite in 2nd trimester maternal hair was margarate, with conflicting results since it was found to be either increased (AUC 0.72, 95%CI 0.58-0.86) [28] or decreased. [18] The N1,N12-diacetylspermine and the perfluorocarboxylic acids were associated to female SGA babies, not males. The former presented a 5-fold decreased risk of SGA across quintiles. The perfluorodecanoic and perfluoroundecanoic acids presented OR of 3.14 (95%CI 1.07-9.19) and 1.83 (95%CI 1.01-3.32). [36] Tyrosine, an essential amino acid for infants, was part of the predictive model of maternal hair, combining 5 metabolites with an AUC of 0.998 (95%CI 0.992-1.0) [18]. However,

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Table 3. Predictive metabolites summarized according to their chemical class, subclass, and biological process

| Fatty acyls | | |
|--|---|---|
| | Fatty acids and conjugates | Lipid trans |
| Fatty acyls | Fatty acids and conjugates | Lipid transed of the metabolism, peroxidation; fatty acid metabolism metabolism biosynthesis |
| Fatty acyls | Fatty acids and conjugates | Lipid trans |
| Fatty acyls | Fatty acids and conjugates | Lipid transportemetabolism, peroxidation; lipid metabolis |
| Fatty acyls | Fatty acids and conjugates | Lipid trans |
| Carboxylic acids and derivatives | Amino acids, peptides, and analogues | Catechola in the biosynthesis; phenylalanine and tyrosine metabolism in the provide hormone synthesis; transcription and translation in translation in the provide hormone synthesis; transcription and translation in the provide hormone synthesis; transcription and translation in the provide hormone synthesis; transcription and translation is the provide hormone synthesis; translation is the provide hormone synthesis; translation is the provide hormone synthesis; transcription and translation is the provide hormone synthesis; translation is the provide hormone synthes; translation |
| Carboxylic acids and derivatives | Amino-acids, peptides, and analogues | Glycine and serine metabolism; methionine metabolism |
| Carboxylic acids and derivatives | Dicarboxylic acid and derivatives | Fatty acid biosonthesis |
| Sphingolipids | Phosphosphingolipids | Sphingolip <mark>e</mark> l signalling pathway, nneuroactive ligand- receptor interaction |
| Sphingolipids | Phosphosphingolipids | Lipid metagolism pathway, sphingolipid metabolism |
| Alkyl halides | Alkyl fluorides | Not reported ^b 3 |
| Alkyl halides | Alkyl fluorides | Not reported b |
| Steroids and steroids derivatives | Vitamin D and derivatives | Lipid metagolisin pathway |
| Glycerolipids | Diradylglycerols | Adipocytolane gignaling pathway |
| Hydroxy acids and derivatives | Alpha hydroxy acids and derivatives | Gluconeogenesis, glycogenosis types IB and IC, pyruva metabolisr, trasephosphate isomerase |
| Carboximidic acids and derivatives | Carboximidic acids | hn 1 |
| Glycerophospholipids | Glycerophosphocholines | Not reported Not |
| Saturated hydrocarbons | Alkanes | Not report a b |
| Keto acids and derivatives | Gamma-keto acids and derivatives | Not reported b |
| ants. º No human metabolic pathways re | ported at KEGG. PFDeA: perfluorodecand | oic acid; PFUnDA: perfluoroundecanoic acid. |
| | Fatty acyls Fatty acyls Carboxylic acids and derivatives Carboxylic acids and derivatives Sphingolipids Sphingolipids Alkyl halides Alkyl halides Steroids and steroids derivatives Glycerolipids Hydroxy acids and derivatives Glycerophospholipids Saturated hydrocarbons Keto acids and derivatives Ints. ^b No human metabolic pathways reference | Fatty acylsFatty acids and conjugatesFatty acylsFatty acids and conjugatesCarboxylic acids and derivativesAmino acids, peptides, and analoguesCarboxylic acids and derivativesAmino-acids, peptides, and analoguesCarboxylic acids and derivativesDicarboxylic acid and derivativesSphingolipidsPhosphosphingolipidsSphingolipidsPhosphosphingolipidsSteroids and steroids derivativesAlkyl fluoridesAlkyl halidesAlkyl fluoridesSteroids and steroids derivativesDiradylglycerolsHydroxy acids and derivativesCarboximidic acids and derivativesCarboximidic acids and derivativesAlpha hydroxy acids and derivativesCarboximidic acids and derivativesAlpha hydroxy acids and derivativesAlpha hydroxy acids and derivativesAlpha hydroxy acids and derivativesCarboximidic acids and derivativesAlpha hydroxy acids and derivativesCarboximidic acids and derivativesAlkanes |

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1 Risk of bias and Applicability Concerns

Figure 2 shows synthesized data for all included studies. See Supplementary
Material 2 for individual QUADAS-2 data.

Regarding the risk of bias, all cohort studies conducted a consecutive participant inclusion. [28,33-37,39] Nested case-controls matched cases and controls randomly [33-35,41] or according to maternal and infant characteristics. [17,18,38,42] One study [41] failed to mention matching procedures ('Patient Selection' domain). Researchers were not blinded to SGA status when interpreting metabolomics results, [17,18,41,28,32,35–40] and thresholds of targeted metabolites were not pre-specified [31,33,36,38,39] ('Index Test' domain). Conversely, SGA identification was not influenced by the metabolomics test, although it was unclear when laboratory experiments were performed in some studies. [18,28,31,33,34,41] Birthweight charts were adequate, except for two studies. The first did not report which centile was chosen, [18] and the second used a centile designed for a different population [33] ('Reference Test' domain). Two studies were ranked as 'high risk' because not all participants were included in the analysis [31,37] ('Flow and Timing' domain).

The QUADAS-2 tool also highlights the importance of how the findings of the included studies are suitable to the review question. In the Patient Selection domain, it was ranked as 'high applicability concerns' when infants born between the 4th and the 10th centile, but with normal abdominal circumference growth velocity, were not included in final analysis. [41] It was 'unclear' when the gestational age of maternal assessment was not standardized, [34] or was inferred by hair segment length; [28] or when few metabolites from untargeted studies were chosen for interpretation [41]

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('Index Test' domain). Finally, it was 'high' when the birthweight charts applied did
 not correspond to the study population [18,33] ('Reference Standard' domain).

4 Meta-analysis

From the 15 included studies, only three were designed for prediction purposes [17,18,42] and provided the AUC. The remaining reports described statistical differences of metabolites between SGA pregnancies and controls. [28,31,40,41,32– 39] Accuracy measures were extracted when available (Table 2). However, due to marked heterogeneity (Tables 1 and 2) of gestational age at sampling, type of samples used, type of birthweight chart chosen, thresholds for vitamin D deficiency, metabolomics approach, and identified compounds, a meta-analysis could not be performed.

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14 DISCUSSION

15 Main findings

In this first systematic review of metabolomics and adverse pregnancy endpoints, we presented techniques and metabolites, which were studied for the prediction of SGA. Any effect on birthweight has important implications for perinatal research, since it is related to short and long-term outcomes, [43-46] and in different generations. [47,48] Intrauterine environment influences fetal growth through epigenetic processes: altered gene expression potentially leads to distinct phenotypes. [49] Metabolomics is the most adequate approach to study this outcome, since it is most directly related to phenotype. [50]

Interpretation of metabolomics findings in pregnancy can be challenging.
 Firstly, maternal metabolites concentrations are influenced by placental transfer to

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and from the fetus. The 'mirror effect', seen for maternal plasma and venous cord blood metabolites at birth, [51] cannot be ruled out when only maternal specimens are studied. Secondly, maternal exposure to distinct compounds may affect metabolite levels. Statistically significant differences between SGA infants and controls may not express the totality of underlying pathological pathways and have no clinical meaning. Finally, it is unclear when the processes leading to SGA are initiated. The disruption in maternal metabolism can theoretically occur at any time. In general the lower the gestational age at which the condition is suspected, the more severe the phenotype will be at birth. [52,53] Thus, the description of clinical data in translational studies must deal with all these confounding factors.

Gestational age at sampling is probably the most important parameter for prediction purposes. With timely prediction, women could be referred to specialized care, have increased surveillance, and this in turn may lead to a reduction in perinatal mortality. There are temporal changes in the maternal metabolome during pregnancy: [28,54–57] therefore, it is reasonable to expect distinctive metabolites at different stages of pregnancy, as reported here. Unfortunately, a wide or unclear definition of gestational age of sampling [34,36,38,40] render a more precise interpretation impossible, and may limit the clinical application of these results.

In contrast, gestational age at birth and birthweight centile seem to be the hallmarks of severity and prognosis of growth restriction. [6,58] Indeed, term and preterm SGA babies show distinct clinical phenotypes, and there are concerns that some babies <10th centile of birthweight are constitutionally small infants. [59–61] If only term deliveries are evaluated, the most severe cases of growth restriction may be potentially missed. Moreover, when term and preterm births are analyzed together, or when lower cutoffs are not specified (e.g. $\leq 3^{rd}$ or $\leq 5^{th}$ centile), the lack of

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predictive metabolites might mean that they are distinct conditions. Thus, we hypothesize that the predictive performance of metabolomics may be improved if data is analyzed by gestational age at delivery, and by different cutoffs of birthweight centiles.

Evidence suggests that tobacco smoke has an impact on birthweight, [62-64] although it is uncertain how and when fetal growth is impaired. It is possibly related to oxidative stress, [65] and both maternal and fetal metabolism may be disturbed at delivery. [66,67] Studies that were included did not investigate cigarette-related chemicals or quantify exposure to tobacco smoke. Therefore, no relationship between SGA and tobacco was found. Hence, we suggest that tobacco interferes with ongoing metabolic pathological processes, or its disturbance is related to additional metabolic pathways other than the one examined by the included studies.

Subgroup and metabolite findings

No reports have explored data on any maternal chronic condition, suspicion of SGA in pregnancy, or number of fetuses. The lack of clear statements about participant selection have hindered data interpretation and precluded these analyses.

The majority of included studies performed a targeted approach, i.e. a hypothesis-testing evaluation, [16,50] driven by epidemiological or experimental data regarding SGA newborns. None of the targeted metabolites [31–40] were in common with those found by 'hypothesis-generating' metabolic profiling [17,18,28,41,42] investigations. This reinforces the suggestion that various maternal metabolic pathways may be triggered by the SGA condition, and be detected by different biological samples. However, since blood is a very complex sample and GC-MS only

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evaluates volatile molecules, [50] therefore our findings may be biased by studymethodologies.

3 Untargeted studies, as expected, have characterized several metabolites 4 that may be validated in future investigations. Nine lipids and fatty acid metabolites, 5 [17,18,28,39] two amino acids, [18,33] and a steroid [17,32] have been identified as 6 potential biomarkers of SGA.

All lipid-related metabolites identified are intermediates for energy storage and breakdown. Most metabolites were found in maternal blood [17] or hair of the SGA group. [18,28] Blood levels of saturated and monounsaturated non-esterified fatty acids apparently remain stable throughout pregnancy, while long chain polyunsaturated fatty acid (DHA and EPA, for example) measurements seem to show ethnicity-related changes. [57] Experimental data shows the importance of hypoxia and oxidative stress to placental function and ultimately, to birthweight. [68,69] Findings from included studies may represent a dysregulation of lipid pathways at the placental level, but an association with maternal background is unclear. Therefore, we hypothesize that disorders of lipid metabolism may be the 'metabolic snapshot' of defective deep placentation, [70] and might reflect maternal efforts to respond to impaired fetal growth.

Recommendations on the assessment of vitamin D and cutoffs to define vitamin D deficiency in pregnancy are controversial. [71] However, vitamin D supplementation decreases SGA risk. [72] In early pregnancy, vitamin D status has been related to SGA, [73,74] which is in accordance with this review, despite the inconsistent findings. [75] There is evidence that trophoblasts actively produce and secrete vitamin D metabolites, [76] but it is not clear how they mediate fetal growth impairment. Altered hepatic gene expression and liver function in vitamin D deficient

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female rats, [77] and single nucleotide polymorphisms [78] in vitamin D receptor
gene have been suggested as mechanisms to be explored by a multidimensional
omics approach.

Finally, homocysteine is an intermediate metabolite of the folate cycle. It is indirectly involved with DNA methylation and is a marker of folate deficiency. [79] Maternal levels rarely reach hyperhomocysteinemia limits, [80] but folate depletion [81–83] and homocysteine itself[80] are thought to be associated with a higher SGA risk. In this review, homocysteine was only statistically different in SGA pregnancies when measured in amniotic fluid, [33] although within the normal ranges proposed for 17-21 weeks. [84] Since amniocentesis is generally performed in women at higher obstetrical risk, future studies should investigate whether homocysteine in amniotic fluid represents a confounding factor or a new biomarker. [85]

14 Methodological quality

Most studies were ranked as 'low risk' of bias or applicability to the review question.
However, the lack of clear descriptions of laboratory experiments, including sample
preparation and storage, and blinding of the researchers to the case/control status,
are major pitfalls of the included studies.

20 Strengths and limitations

To our knowledge, this is the first systematic review of metabolomics and an adverse
pregnancy outcome (SGA). We presented possible biomarkers of SGA
pathophysiology, metabolites implicated in lipid transport and metabolic pathways,
as well as gluconeogenesis.

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However, this analysis has some limitations. First, included studies showed heterogeneity, which is fundamental in systematic reviews. Indeed, there was a wide variety of participant characteristics and methods used, and not all authors provided a detailed description of methods employed. Although the Metabolomics Standard Initiative was released in 2007, [86] there is still poor adherence to guidelines. [87,88] Clear reporting [15,87,88] and data sharing in repositories are crucial steps in identifying features of interest, specifically possible biomarkers to be validated in the clinical studies. [15] Secondly, we could not perform a meta-analysis of the extracted data, impacting the translational potential of metabolomics.

Thirdly, we considered that birthweight was a surrogate measure of intrauterine development. SGA and FGR are not interchangeable concepts. However, SGA has been used as a surrogate for FGR in many clinical studies due to difficulties in defining optimal intrauterine growth: (i) FGR diagnosis relies mostly on ultrasound measurements of fetal biometry, [3,89] which in turn is subject to systematic errors; [90] (ii) intrauterine development is adaptive, rather than uniform [91] or only genetically driven; [49] (iii) growth impairment at birth better identifies adverse neonatal outcomes than during pregnancy. [58] It is recognized that changes in obstetric care occur when growth restriction is suspected, and neonatal outcomes are improved. [21,22] Thus, an accurate prediction of SGA during pregnancy will be a turning point in modern obstetrics.

CONCLUSIONS AND IMPLICATIONS FOR PRACTICE

Using the available clinical tools, efforts to predict SGA remain disappointing. Since SGA is a heterogeneous condition, it benefits from metabolomics. This novel area of research allows analysis of numerous types of biological fluids and detects

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> thousands of metabolites in complex samples. [15,16,25] However, findings of this systematic review must be interpreted with caution. The type of samples used may have influenced LC-MS (2nd trimester maternal blood) and GC-MS (2nd trimester maternal hair) findings in individual studies. Furthermore, the prediction of SGA in the context of maternal disorders, suspected FGR and twin pregnancies is an open field for future metabolomics studies, and environmental exposure investigation as well.

Surprisingly, none of the studies used $\leq 3^{rd}$ centile of birthweight as a cutoff or analyzed preterm deliveries and hypertensive syndromes. Considering our findings and the different phenotypic manifestations of SGA, we envision a better performance when (i) cutoffs other than the 10th centile are tested; (ii) data on gestational age at sampling and at birth are standardized; and (iii) other pregnancysyndromes are considered, especially hypertension. related Thus, future metabolomics results should advance in these critical points.

Finally, all detected biomarkers were related to lipid pathways and energy metabolism. We consider that research efforts to predict SGA should focus on compounds involved in these pathways, up to the 2nd trimester of pregnancy.

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| 58 | 49 | | fetal growth based on serial ultrasound measurements: The Fetal Growth |
| 59 | 50 | | Longitudinal Study of the INTERGROWTH-21st Project. Lancet |
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1 AUTHORS CONTRIBUTIONS

DFBL and ACM have equally contributed to this report, and both are guarantors of this review. They elaborated the protocol, searched the literature, selected studies, extracted data, assessed risk of bias, and drafted the initial manuscript. RTS and EFMJ have participated in judging inclusion of studies, interpreting data, and revising the manuscript. FM have supported data extraction and have critically examined the clinical interpretation of results. ASK has discussed the quantitative data synthesis, and supervised the report writing. PNB, LCK, and JGC have supervised and approved all steps. All authors have read and agree with this submission.

11 ACKNOWLEDGEMENTS

We are grateful to (i) Shauna Barret, from the Brookfield Library, University College Cork, Ireland, for her support with the literature search; (ii) Ting-Li Han, from the Department of Obstetrics, The First Affiliated Hospital of Chongqing Medical University, China, for providing additional data for this systematic review; (iii) and Luis Felipe D'Orsi, from University of Campinas, for his support with methods' issues.

19 FUNDING

DFBL (process number 88881.134512/2016-01) and RTS (88881.134095/2016-01) have awarded scholarships from Brazilian Federal Agency for Support and Evaluation of Graduate Education (CAPES). ACM was granted a scholarship from Science Foundation Ireland, for her doctoral thesis. PRETERM-SAMBA has granted sponsor from Brazilian National Research Council (CNPq) (Award 401636/2013-5) and from the Bill and Melinda Gates Foundation (grant OPP1107597), corresponding 1 2 З

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to the research call "Grand Challenges Brazil: Reducing the burden of preterm birth", 1 2 number 05/2013. This research received no specific grant from commercial or not-3 for-profit sectors. Our sponsors have not intervened in authors' decision to write the 4 systematic review protocol or to submit this paper. 5 6 **COMPETING INTERESTS** 7 None to declare. 8 9 **PROVENANCE AND PEER REVIEW** 10 Not commissioned; externally peer reviewed. 11 12 **Figure captions** 13 Figure 1. PRISMA flowchart of study identification, screening and selection. From: 14 15 Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA 16

17 Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097. For more

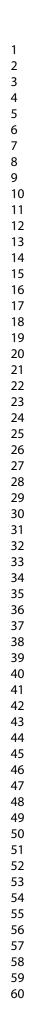
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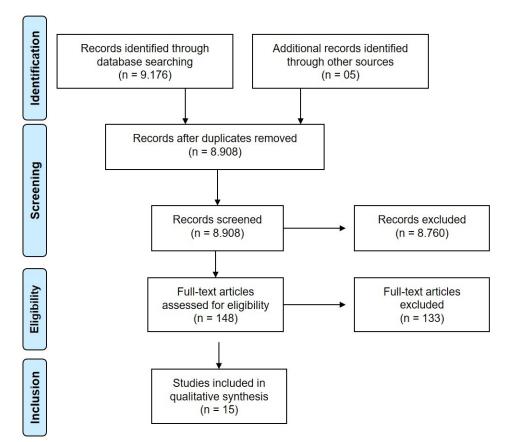
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Figure 2. Assessment of risk of bias (A) and applicability concerns (B) of individual 20 21 studies.

- 23 Supplementary material description
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 - 25 Supplementary material 2 - Individual QUADAS-2 data for all 15 included studies.

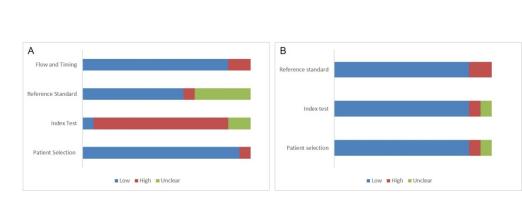






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| Barnes CM et al, 2010 | United States | Maternal samples collected at delivery. | |
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51 of 55 BMJ Open Examining the predictive accuracy of metabolomics for small for gestational age babies a systematic review Debora F. B. Leite & Aude-Claire Morillon, Elias F. Melo Júnior, Renato T. Souza, Fergus P. McCarthy, Ali S. Khashan, Phile N. Baker, Louise C. Kenny, José Guilherme Cecatti. Supplementary material 2 - Individual QUADAS-2 data for all 15 included studies.

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| 21 | Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 5 |
| 22 23 24 | Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants in prventions, comparisons, outcomes, and study design (PICOS). | 6 |
| 25 | METHODS | - | ng, g | |
| 26 27 28 | Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and if available, provide registration information including registration number. | 6 |
| 29 30 | Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 7-8 |
| 31 32 33 | Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with stady authors to identify additional studies) in the search and date last searched. | 6-7/ 9 |
| 34 35 | Search | 8 | Present full electronic search strategy for at least one database, including any limits use, such that it could be repeated. | 6-7 |
| 36 37 39 | Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 7-8 |
| 39 40 | Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplic te) and any processes for obtaining and confirming data from investigators. | 8 |
| 41 42 | Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 7-8 |
| 43 44 45 | Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome, level, and how this information is to be used in any data synthesis. | 8-9 |



PRISMA 2009 Checklist

BMJ Open **IA 2009 Checklist** Examining the predictive accuracy of metabolomics for small for gestational age babies: a systematic review

| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 9 |
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| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including take asures of consistency (e.g., I ²) for each meta-analysis. | 9 |
| | • | Page 1 of 2 | 1 |
| Section/topic | # | Checklist item | Reported on page # |
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 8-9 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regionsion), if done, indicating which were pre-specified. | 7 |
| RESULTS | | Al m | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 9 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PLCOS, follow-up period) and provide the citations. | 9-13 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessme | 23-24 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot | 20-22 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measure of consistency. | 24 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 9; 23-24 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | NA |
| DISCUSSION | <u> </u> | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 24-28 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., if complete retrieval of identified research, reporting bias). | 28-29 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implication by future research. | 29-30 |

| Pa | age 55 of 55 | BMJ Open de | |
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| 1 2 | |)9 Checklist | |
| 2 3 4 | Examin | 딸 ଡ଼ ing the predictive accuracy of metabolomics for small for gestational age babies: a systematic review | |
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Examining the predictive accuracy of metabolomics for small for gestational age babies: a systematic review

| Journal: | BMJ Open |
|--------------------------------------|---|
| Manuscript ID | bmjopen-2019-031238.R1 |
| Article Type: | Research |
| Date Submitted by the Author: | 13-Jul-2019 |
| Complete List of Authors: | Leite, Debora; Campinas' State University, Department of Tocogynecology; Universidade Federal de Pernambuco, Morillon, Aude-Claire; University College Cork National University of Ireland, Irish Centre for Fetal and Neonatal Translational Research (INFANT) Melo Júnior, Elias; Universidade Federal de Pernambuco, Clinics Hospital Souza, Renato; Universidade Estadual de Campinas, Obstetrics and Gynecology; McCarthy, F. P.; St Thomas Hosp Khashan, Ali; University College Cork, Department of Epidemiology and Public Health Baker, Philip ; University of Leicester, College of Medicine Kenny, Louise; University of Liverpool School of Life Sciences, Department of Women's and Children's Health Cecatti, Jose; University of Campinas, Obstetrics and Gynecology |
| Primary Subject Heading : | Obstetrics and gynaecology |
| Secondary Subject Heading: | Epidemiology |
| Keywords: | small for gestational age, fetal growth restriction, metabolomics, gas- chromatography, mass spectrometry |



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| 3 4 5 | 1 | RESEARCH ARTICLE: SYSTEMATIC REVIEW |
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| 6 7 | 2 | Examining the predictive accuracy of metabolomics for small for gestational |
| 8 9 10 | 3 | age babies: a systematic review |
| 11 12 | 4 | |
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| 9 | |
| 10 | Word Count: |
| 11 | Abstract: 289 words |
| 12 | Main text 4,167 words |
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1 ABSTRACT

Introduction: To date, there is no robust enough test to predict small for gestational
age (SGA) infants, which are at increased life-long risk of morbidity and mortality.

4 **Objective**: To determine the accuracy of metabolomics in predicting SGA babies and

5 elucidate which metabolites are predictive of this condition.

Data sources: Two independent researchers explored 11 electronic databases and
grey literature in February 2018 and November 2018, covering publications from
1998 to 2018. Both researchers performed data extraction and quality assessment
independently. A third researcher resolved discrepancies.

Study eligibility criteria: Cohort or nested case-control studies were included, which
 investigated pregnant women and performed metabolomics analysis to evaluate SGA
 infants. The primary outcome was birthweight <10th centile - as a surrogate for fetal
 growth restriction - by population-based or customized charts.

Study appraisal and synthesis methods: Two independent researchers extracted
data on study design, obstetric variables and sampling, metabolomics technique,
chemical class of metabolites, and prediction accuracy measures. Authors were
contacted to provide additional data when necessary.

Results: A total of 9,181 references were retrieved. Of these, 273 were duplicate, 18 19 8,760 were removed by title or abstract, and 133 were excluded by full text content. Thus, 15 studies were included. Only two studies used the 5th centile as a cutoff, and 20 most reports sampled 2nd trimester pregnant women. Liquid-chromatography coupled 21 22 to mass spectrometry was the most common metabolomics approach. Untargeted studies in the 2nd trimester provided the largest number of predictive metabolites, 23 using maternal blood or hair. Fatty acids, phosphosphingolipids, and amino acids 24 25 were the most prevalent predictive chemical subclasses.

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Conclusions and Implications: Significant heterogeneity of participant characteristics and methods employed among studies precluded a meta-analysis. Compounds related to lipid metabolism should be validated up to the 2nd trimester in different settings.

5 Systematic review registration number: CRD42018089985.

Keywords: small for gestational age, fetal growth restriction, metabolomics,
prediction, gas-chromatography, mass spectrometry, vitamin D, homocysteine, lipids,
fatty acids.

10 STRENGHTS AND LIMITATIONS OF THIS STUDY

- To our knowledge, this is the first systematic review to assess the predictive accuracy of metabolomics for an adverse pregnancy outcome.
- Using SGA as surrogate for fetal growth restriction just as in epidemiological investigations – improves the translational potential of metabolomics.
- Identification of techniques, types of maternal samples and chemical classes paves the way for future metabolomics investigations on fetal growth patterns.
- include accuracy measures of individual metabolites or chemical subclasses in
 predicting SGA.

Available data could not support a meta-analysis; further studies should

ORIGINAL PROTOCOL: Leite DFB, Morillon A-C, Melo Júnior EF, *et al.*Metabolomics for predicting fetal growth restriction: protocol for a systematic review
and meta-analysis. *BMJ Open* 2018;8:e022743. doi:10.1136/bmjopen-2018-022743.

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1 INTRODUCTION

Fetal growth restriction (FGR) and small for gestational age (SGA) infants are major concerns in modern obstetrics. [1–3] SGA is commonly used as a proxy for FGR, [4] despite the subtle differences between these two pathological conditions. The prevalence of both varies according to criteria applied and on the population and setting, although it reaches as much as 25% in low and middle-income countries. [5] SGA newborns may have adverse health effects, such as stillbirth, [4] perinatal asphyxia, [6] impaired neurodevelopment, [7] and increased cardiovascular risk. [8,9] To date, there are no robust prediction tools for SGA using clinical factors, [10,11] ultrasound data, [12,13] or placental biomarkers. [14]

For hypothesis generating or validation purposes, metabolomics is a novel area of biomarker, discovery, development and clinical diagnostics in translational medicine. [15,16] Metabolomics is the study of all metabolites [15,16] in a given sample, i.e. low molecular weight compounds (50-2000 Da) that are intermediates of biochemical reactions and metabolic pathways, considered to directly reflect cellular activity and phenotype. [15,16] Recent studies have evaluated the pathophysiology [17-20] of SGA with metabolomics. However, little is known about the potential of metabolomics to identify predictive compounds of SGA.

Since metabolomics can identify multiple metabolites from low volume
samples, and create a model from a collection of these samples, [15] it is a promising
technology for hypothesis generation in a heterogeneous condition such as SGA.
The prediction of SGA in pregnancy would help refer women to specialized care
facilities, improving maternal and neonatal outcomes. [21,22]

In this context, our review question was "What is the accuracy of metabolomics for predicting FGR?". Then, the main objective of this systematic

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review was to assess the accuracy of metabolomics techniques in predicting SGA.
 As a secondary aim, we intended to determine which metabolites are predictive of
 this condition.

5 METHODS

6 The protocol for this systematic review was published previously. [23] This study 7 follows international guidelines for transparency (PROSPERO, CRD 42018089985) 8 and respects the Preferred Reporting Items for Systematic Reviews and Meta-9 Analysis (PRISMA) statement. [24] For this systematic review, ethical approval was 10 unnecessary.

12 Literature Search Strategy

Two independent researchers (DFBL and ACM) assessed 11 electronic databases (PubMed, EMBASE, Latin American and Caribbean Health Sciences Literature (LILACS), Scientific Electronic Library Online (Scielo), Health Technology Assessment (HTA), Database of Abstracts of Reviews of Effects (DARE), Aggressive Research Intelligence Facility (ARIF), Cumulative Index of Nursing and Allied Health Literature (CINAHL), Maternity and Infant Care (MIDIRS), Scopus, and Web of Science) and grey literature. There were no limits or language constraints; the search strategy covered published documents between 1998 and 2018. Keywords 'small for gestational age', 'metabolomics', 'prediction', 'antenatal', and variations of each, were combined with Boolean operators depending on each database requirements. The full EMBASE literature search was, as follows: ('fetal growth retardation' OR 'fetal growth restriction' OR 'intrauterine growth restriction' OR 'intrauterine growth retardation' OR 'small for gestational age') AND ('metabolomic*' OR 'metabonomic*'

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OR 'metabolit* 'H NMR' OR 'proton NMR' OR 'proton nuclear magnetic resonance'
OR 'liquid chromatogra*' OR 'gas chromatogra*' OR 'UPLC' OR 'ultra-performance'
OR 'ultra performance liquid chromatograph*') AND ('pregnan*' OR 'antenat*' OR
'ante nat*' OR 'prenat*' OR 'pre nat*') AND ('screen*' OR 'predict*' OR 'metabolic
profil*'). Please check Supplementary Material 1 for more details.

7 Outcomes and subgroup analysis

8 The primary outcome was SGA, as a surrogate for FGR and defined as birthweight
9 <10th centile, by population-based or customized charts. Secondary outcomes were
10 birthweight ≤5th or ≤3rd centile.

11 The intended subgroup analysis comprised: type of metabolomics technique 12 applied (nuclear magnetic resonance, NMR; gas or liquid chromatography coupled 13 with mass spectrometry, GC-MS or LC-MS respectively); maternal health status 14 before pregnancy (women with *versus* without any chronic health condition); type of 15 SGA suspected during pregnancy (early *versus* late SGA); and type of pregnancy 16 (singleton *versus* multiple pregnancy).

18 Selection Criteria of Studies, Data Collection and Analysis

19 Cohort or case-control studies were included if maternal samples were collected 20 before the clinical diagnosis of SGA, if any metabolomics technique was applied, and 21 if the results of SGA were presented. Articles presenting data from the same 22 research project but analyzing distinct metabolites or showing data from different 23 countries were included. Studies were excluded (i) according to study design; (ii) if 24 they had not applied any metabolomics technique; (iii) if they were only experimental 25 studies; (iv) if it was not possible to extract data on SGA; (v) or if they presented

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duplicate data, in which case the most complete publication was included for final analysis.

Two researchers (DFBL and ACM) independently selected studies, extracted
data and discussed discrepancies. One additional reviewer (EFMJ or RTS) helped to
decide, by majority, when no consensus was reached.

6 Piloted standardized forms were applied for data extraction, including 7 pregnancy characteristics and experimental details. The Human Metabolome 8 Database (HMDB) [25] and the Kyoto Encyclopedia of Genes and Genomes [26] 9 were used for matching chemical class and metabolic pathways of each metabolite, 10 respectively.

12 Risk of bias and Assessment of concerns regarding applicability

Two researchers (DFBL and ACM) independently evaluated individual studies using
the QUADAS-2 tool. [27] One of the third reviewers (EFMJ, or RTS) helped in
decision-making when no consensus was achieved.

Each study was classified as high, low, or unclear risk of bias in four Domains (Patient Selection, Index Test, Reference Standard, and Flow and Timing), and as high, low, or unclear concerns regarding applicability in the first three Domains. We did not consider two signaling guestions ("Was a case-control design avoided?", "Was there an appropriate interval between the index test and reference standard?"). The nested case-control design was an inclusion criterion and maternal samples should have been collected during pregnancy, i.e. before the SGA diagnosis. Studies were considered 'low risk', for example, (i) if pregnancy or neonatal complications were not excluded in just one group of participants or data on participant selection had been provided; (ii) if methods for sample preparation and

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interpretation were standardized or metabolite threshold was defined before the
experiments (for targeted analysis); (iii) if the adequacy and reasons for choosing the
reference birthweight chart had been explained; or, (iv) if large for gestational age
babies had been excluded from the final comparative analysis.

6 Data synthesis

A quantitative summary of data was performed when any predictive accuracy measures could be extracted. Authors were contacted to provide additional information, when necessary. However, only Delplancke et al [28] replied. The estimation of likelihood ratios and hierarchical summary receiver operator characteristic curve [29] were planned, as well as assessment of heterogeneity and publication bias. [30] However, due to lack of data, a meta-analysis could not be performed.

15 Patient and Public Involvement

16 There was no patient or public involvement in conducting this systematic review.

18 Data Availability Statement

All data relevant to this systematic review are included in this manuscript - in the
article or uploaded as supplementary information. There are no individual patient
identifiable data.

RESULTS

24 Literature search characteristics

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The literature search for this systematic review was performed in February 2018, and re-run in November 2018. A total of 9,181 references were retrieved (Figure 1). After the removal of duplicate records (n=273), title and abstract screening, and analysis of the remaining 148 full-text articles, 15 articles were included. [17,18,28,31–42] See Supplementary Material 2 for excluded studies.

Characteristics of the included studies

The characteristics of the included studies are shown in Table 1. The prevalence of SGA ranged from 7.3% [33] to 21.5% in cohort studies. [28] There were no studies using a birthweight $\leq 3^{rd}$ centile for a definition of SGA. The time interval between initial participant enrollment and publication varied from three [17] to 54 years, [40] although these data were unclear in 38% of the reports. [18,28,32,33,37] In nested case-control studies, participants were matched by maternal age, [17,18,38,42] ethnicity, [17,18,42] parity, [38] body mass index, [17,18,42] or infant gender. [18,38] Participant characteristics varied between studies. Regarding gestational age at assessment, samples were collected in the 2nd trimester in one half of the studies. [17,18,33,35,37,39,42] In three reports, women were assessed at least twice. [34,38,41] In one study, maternal blood was drawn either in the 1st or 2nd trimester; [40] and in another three studies, only samples from the 3rd trimester were considered. [28,36,41] In the latter case, maternal hair was divided according to length, allowing evaluation of 2nd and 3rd trimester metabolites. [28] Studies considering the 5th centile as the cutoff, sampled women in the 1st trimester. [31,32] Twin pregnancy was a clear exclusion criterion in most studies. [17,18,31,33-35,37,40-42] Pregnancy aided by assisted reproduction [18,37] or women with pre-existing conditions [17,18,35,37,42] were also excluded, although these data were

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incompletely reported. [28,32,36,38,39,41] When both nulliparous and multiparous women were enrolled, there was no data analysis according to parity. Half of the studies considered term deliveries exclusively, [18,28,36,38-41] and the remaining studies did not differentiate results according to gestational age at birth. Regarding clinical risk factors for SGA, only one paper mentioned a previous history of SGA, but findings were not adjusted for this variable. [32] All studies, except one, [28] cited participant smoking status. The rate of smoking habit ranged from 2.4% [18] to 47.5%. [40] It is important to note that Gernand et al [40] analyzed samples from women recruited between 1959 and 1965, when smoking while pregnant was encouraged, which explains the high rate of smoking participants. The duration of smoking or any differences in birthweight (absolute measures or centiles) were not clearly stated. Although more prevalent in SGA pregnancies, results did not change with this variable control. [31,32,35,37,40] Only Gong et al [41] mentioned the suspicion of SGA in pregnancy, exhibiting decreasing abdominal circumference growth velocity between 20-36 wks. However, on final analysis, these babies were grouped with infants not suspected during pregnancy.

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| Table ² | 1. Main characteristics of | included stuc | lies | | | mjopen-2019-031238 I by copyright, inclu | | |
|------------------------------|---|----------------------------|-------------------------------|---|--|--|----------------------------|---|
| Authors, year | Country, year of participants enrolment | Study design | Affected/ non- affected | Gestational age at assessment | Type of pregnancy | ing Parity for usg | Birthweight curve | - |
| Outcome: SGA | <5 th centile | | | | | gust 20 inseigr | | - |
| Costet N et al, 2011 | France, 2002-2006 (PELAGIE Cohort) | Nested case- control | 134/ 399 | 11w | Single pregnancy | Nulliparous wormen, unclear | Customized curve | - |
| Ertl R et al, 2012 | United Kingdom ^a | Nested case- control | 150/ 1,000 | 11 ⁺⁰ -13 ⁺⁶ w | Unclear | 55,2 % Bulliparous in SGAS Croup, 48.1% null a gous in control | Population-based charts | - |
| Outcome: SGA | <10 th centile | | | The second | | tp://br) - ing, A | | - |
| Grandone E et al, 2006 | Italy ^a | Cohort | 31/ 393 | 17.1 ± 1.2w ^b (mean) | Single pregnancy; no maternal pre-existing conditions | training, a | Population-based charts | - |
| van Eijsden M et al, 2008 | Netherlands, 2003- 2004 (ABCD Study) | Cohort | 429/ 3275 | 13.5 ± 3.3w (mean) | Term deliveries, no diabetes or hypertension | 57:6% nulliparous | Population-based charts | - |
| Horgan RP et al, 2011 | Australia, 2008-2011 (SCOPE Cohort) | Nested case- control | 40/ 40 | 14-16w | Single pregnancy; no other pregnancy complications | technolog 3, 20 | Customized curve | - |
| Gernand AD et al, 2013 | United States, 1959- 1965 (Collaborative Perinatal Project) | Nested case- control | 395/ 1751 | ≤26w | Single pregnancy; term deliveries | Parous women Parous women A Ge | Population-based charts | - |
| Sulek K et al, 2014 | Singapore ^a (GUSTO Study) | Nested case- control | 41/ 42 | 26-28w | Single pregnancy; term deliveries; no maternal pre-existing conditions | Nulliparous women, unclear proportions | Population-based charts | - |
| Choi R et al, 2016 | South Korea, 2012- 2013 | Cohort | 39/ 217 | 1 st , 2 nd or 3 rd trimester | Single pregnancies | Nulliparo∰s and parous wom€n, unclear | Population-based charts | - |

| Page | 13 of 56 | | | | BMJ C | Dpen | mjopen-2019-0 d by copyright, | |
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| 6 7 8 9 | Kiely ME et al, 2016 | Ireland, 2008-2011 (SCOPE Cohort) | Cohort | 190/ 1578 | 14-16w | Single pregnancy; no maternal pre-existing conditions | for uses r | Customized curve |
| 10 11 12 | Ong YL et al, 2016 | Singapore ^a (GUSTO Study) | Cohort | 83/ 827 | 26-28w | Single pregnancy; no maternal chronic illness | 4 4 4 4 4 4 4 5 7 7 7 7 7 7 7 7 7 7 7 7 | Population-based charts |
| 13 14 15 16 | Wang Y et al, 2016 | Taiwan, 2000-2001 (Taiwan Maternal and Infant Cohort Study) | Cohort | 35/ 188 | 3 rd trimester | Unclear; term deliveries | text 40 40 and dar dar dar dar dar dar dar dar dar dar | Population-based charts |
| 17 18 19 20 | Delplancke TDJ et al, 2018 | New Zealand ^a | Cohort | 20/ 73 | 34-37w | Unclear; term deliveries | ino ino ABES ABES | Customized curve |
| 21 22 23 | Luthra G et al, 2018 | United States, 2010- 2012 (TIDES Study) | Nested case- control | 53/ 106 | 1 st and 2 nd trimester | Single pregnancies; term deliveries | A m 69% oulliparous nin p ning, br | Customized curve |
| 24 25 26 27 | Gong S et al, 2018 | United Kingdom, 2008- 2012 (POP study) | Nested case- control | 162/259 | 36w | Single pregnancies; term deliveries | and Nutiparous simila | Customized curve |
| 28 29 30 31 32 | Morillon A-C et al, 2018 | 2008-2011 (SCOPE Study) | Nested case- control | 40/40 | 20w | Single pregnancies | Jumparous Jumparous r technologies | Customized curve |
| 33 34 | ^a Unclear period | d of participant recruitment. | ^b Mean for | all study partic | pants. | | at | |
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1 Subgroup analysis

Due to unavailable data, the only subgroup analysis performed was related to the metabolomics approach applied (Table 2). There was no mention of adherence to metabolomics reporting data guidelines. LC-MS was the leading technique used. Three studies have investigated metabolites related to environmental exposure, from contaminated water, [31] consumer products, [36] or pesticides, [42] while others have analyzed endogenous compounds. [32-35,37-40] Only Luthra et al conducted a biomarker validation study, [38] while Gong et al [41] chose to analyze the top ten statistically different metabolites according to infant sex.

Maternal blood was the most common biological sample analyzed by LC-MS in all studies, [17,32,34–37,39–41] except for one, which used GC-MS.[39] Maternal urine was analyzed by NMR, [38] GC-MS [36] or LC-MS. [42] There was only one report using amniotic fluid [33] and two using maternal hair, [18,28] all applying GC-MS. The period of laboratory analysis was rarely specified, which made it impossible to estimate total time of sample storage.

Untargeted studies reported diverse metabolic features. Authors matched the peaks with an in-house library [18,28] or HMDB-related database. [17,42] Horgan et al [17] found 785 compounds both in maternal and newborn samples; their predictive model included 19 metabolites (only five could be putatively identified, Table 2) and used 2nd trimester maternal blood. Sulek et al [18] and Delplancke et al [28] prepared and analyzed samples with GC-MS using similar protocols. Sulek et al [18] identified 32 statistically different chromatographic features from which they built a (2predictive model using five metabolites. including two fatty acids methyloctadecanoate and margarate). In contrast, Delplancke et al, [28] identified 198 metabolites, including three fatty acids (margaric, pentadecanoic, and myristic acid) showing significantly higher levels in SGA cases, when 2nd trimester maternal hair segments were studied. to occurrence on the occurrence of the occurrenc

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| group analysis of included stud Metabolomics Technique | lies according to Maternal sample/ Storage temperature | which metabole Prediction model* | omics technique wa Targeted compounds | as applied. Coefficient of variation/ Limits of quantitation | on 10 pe ling for the second Predictive composition of the second composition of the second comp | Sensitivity/ Specificity | AUC | |
| netic resonance | | | | | nent d to t | | | |
| ¹ H-NMR 1D NOESY with pre-saturation and homonuclear 2D <i>J</i> -resolved at 300 K Bruker 600 MHz Advance III HD spectrometer | Urine/ -80°C | Targeted | Tyrosine, acetate, formate, trimethylamine | NA | wnloaded from http Superieur (ABES) textoand data minin | | | |
| ography coupled to mass spe | ectrometry | | 6 | | g, Al ti | | | |
| GC-MS Simple head space SPME- Capillary GC | Urine/ -20°C | Targeted | Trichloroacetic acid | <5%/ 0.01mg/L | ainanen. Nang, and | 0.1/ 0.93 | | |
| GC-MS Thermo Trace GC Ultra system coupled to ISQ mass selective detector Capillary GC column: Phenomenex ZB-1701 (30 m x 250 µm id x 0.15 µm with 5 m guard column) | Hair/ -20°C | Untargeted | NA | NA | ↓ Lactate ↓ Lectulinate ↑2-methyloctatecanate ↑Typosite ↓ Maggarate | | 0.998 | |
| GC-MS: Agilent 7890B gas chromatograph, capillary column ZB-1701 (30m x 250µm id x 0.15µm with 5m guard column) 5977 A mass spectrometer, electron impact ionisation | Hair/ -20ºC | Untargeted | NA | NA | ↑ Margarice ↑ Pentadecare ↑ Myristic acid ↑ Myristic acid ^c f ographique | | 0.72 0.73 0.73 | |
| r | Metabolomics Technique netic resonance ¹ H-NMR 1D NOESY with pre-saturation and homonuclear 2D J-resolved at 300 K Bruker 600 MHz Advance III HD spectrometer ography coupled to mass spectrometer ography coupled to mass spectrometer GC-MS Simple head space SPME- Capillary GC GC-MS Thermo Trace GC Ultra system coupled to ISQ mass selective detector Capillary GC column: Phenomenex ZB-1701 (30 m x 250 µm id x 0.15 µm with 5 m guard column) GC-MS: Agilent 7890B gas chromatograph, capillary column ZB-1701 (30m x 250µm id x 0.15µm with 5m guard column) 5977 A mass spectrometer, | Metabolomics Technique Maternal sample/ Storage temperature Metabolomics Technique Urine/-Storage temperature Metabolomics Technique Urine/-80°C Metabolomics Technique Urine/-80°C Image: Maternal space SD J-resolved at 300 K Urine/-80°C Bruker 600 MHz Advance III HD spectrometer Urine/-20°C Graphy coupled to mass spectrometry Urine/-20°C GC-MS Hair/-20°C GC-MS Hair/-20°C GC-MS Hair/-20°C GC-MS: Hair/-20°C Agilent 7890B gas Hair/-20°C < | Metabolomics Technique Maternal sample/ Storage temperature Prediction model* Prediction model* Prediction model* Prediction model* Pretic resonance Urine/ -80°C Targeted 1H-NMR 1D NOESY with pre-saturation and homonuclear 2D J-resolved at 300 K Urine/ -80°C Targeted Bruker 600 MHz Advance III HD spectrometer Urine/ -20°C Targeted ography coupled to mass spectrometry Urine/ -20°C Targeted GC-MS Simple head space SPME- Capillary GC Urine/ -20°C Targeted GC-MS Simple head space SPME- Capillary GC Hair/ -20°C Untargeted GC-MS Thermo Trace GC Ultra system coupled to ISQ mass selective detector Capillary GC column: Phenomenex ZB-1701 (30 m x 250 µm id x 0.15 µm with 5 m guard column) Hair/ -20°C Untargeted GC-MS: Agilent 7890B gas chromatograph, capillary column ZB-1701 (30m x 250µm id x 0.15µm with 5m guard column) Hair/ -20°C Untargeted Storp id x 0.15µm with 5m guard column) Hair/ -20°C Untargeted | group analysis of included studies according to which metabolomics technique was ample/storage temperature Prediction model* Targeted compounds Metabolomics Technique Maternal sample/Storage temperature Prediction Targeted compounds netic resonance Urine/-80°C Targeted Tyrosine, accetate, formate, trimethylamine 1H-NMR 1D NOESY with pre-saturation and homonuclear 2D J-resolved at 300 K Urine/-80°C Targeted Tyrosine, accetate, formate, trimethylamine Bruker 600 MHz Advance III HD spectrometer Urine/-20°C Targeted Trichloroacetic acid GC-MS Urine/-20°C Targeted NA GC-MS Hair/-20°C Untargeted NA Thermo Trace GC Ultra system coupled to ISQ mass selective detector Capillary GC column: Phenomenex ZB-1701 (30 m x 250 µm id x 0.15 µm with 5 m guard column) Hair/-20°C Untargeted NA GC-MS: Agilen 7890B gas chromatograph, capillary column ZB-1701 (30 m x 250 µm id x 0.15 µm with 5 m guard column) Hair/-20°C Untargeted NA Storage column Hair/-20°C Untargeted NA Storage column Hair/-20°C NA NA Storage column Storage column Storage column Storage column Storage column | group analysis of included studies according to which metabolomics technique was applied. 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| atography coupled to mass s | spectrometry | | | | includi | 2 | | |
| LC-MS/MS triple quadrupole Applera API 3000, TurbolonSpray ionisation | Amniotic fluid/ -80°C | Targeted | Homocysteine | Unclear | لم Homocyster †Homocyster 1,05-£عي | 3∭) 5 | | |
| UPLC- MS/MS Thermo Fisher LTQ Orbitrap, ESI | Plasma/ - 80ºC | Untargeted | NA | NA | Hexacosa diglyce phosphoen | eic acid, yso- line, | | 0.90 |
| HPLC- MS/MS Shimadzu Prominence HPLC system with a column Phenomenex Luna C8 3 x 50 mm; AbSciex API-5000 triple quadrupole, ESI | Serum/ -80°C | Targeted | 25(OH)D _{2;} 25(OH)D ₃ | 6.3% ^a , 6.6% ^b (D ₂); 6.5% ^a , 7.3% ^b (D ₃)/ unclear | (12.16nğ/mL 20.54fig/a ini g, an | \$8.09- L) | 0.72/ 0.45 | |
| LC-MS/MS | Serum/ -20°C | Targeted | 25(OH)D _{2;} 25(OH)D ₃ | 8.2% ^a (D ₂) 5.9% ^a (D ₃)/ <1ng/mL | sime Najiar teo | | 0.39/ 0.66 | |
| HPLC- MS/MS Waters HPLC system, Applied Biosystems API- 4000 MS/MS mass spectrometer | Serum/ -20°C | Targeted | Methylmalonic acid; homocysteine | <10%ª; <10% ^b / Unclear | No logies. | 13 2025 at | | |
| UPLC- MS/MS Waters Acquity UPLS system, Waters Triple Quadrupole TQD mass spectrometer | Serum/ -80°C | Targeted | 25(OH)D ₂ ; 25(OH)D ₃ ; 3-epi-25(OH)D ₃ . | <6% ^a ; <5% ^b / 0.57ng/mL (D ₂); 0.26ng/mL (D ₃), 0,41ng/mL (epi-D ₃) | None | nce | | |
| - II | LC-MS/MS triple quadrupole Applera API 3000, TurbolonSpray ionisation UPLC- MS/MS Thermo Fisher LTQ Orbitrap, ESI HPLC- MS/MS Shimadzu Prominence HPLC system with a column Phenomenex Luna C8 3 x 50 mm; AbSciex API-5000 triple quadrupole, ESI LC-MS/MS HPLC- MS/MS Waters HPLC system, Applied Biosystems API- 4000 MS/MS mass spectrometer UPLC- MS/MS Waters Acquity UPLS system, Waters Triple Quadrupole | triple quadrupole Applera API 3000, TurbolonSpray ionisationfluid/ -80°CUPLC- MS/MS Thermo Fisher LTQ Orbitrap, ESIPlasma/ - 80°CHPLC- MS/MS Shimadzu Prominence HPLC system with a column Phenomenex Luna C8 3 x 50 mm; AbSciex API-5000 triple quadrupole, ESISerum/ -80°CLC-MS/MSSerum/ -20°CHPLC- MS/MS spectrometerSerum/ -20°CUPLC- MS/MS Waters HPLC system, Applied Biosystems API- 4000 MS/MS mass spectrometerSerum/ -20°CUPLC- MS/MS Waters Acquity UPLS system, Waters Triple QuadrupoleSerum/ -80°C | LC-MS/MS triple quadrupole Applera API 3000, TurbolonSpray ionisationAmniotic fluid/ -80°CTargetedUPLC- MS/MS Thermo Fisher LTQ Orbitrap, ESIPlasma/ - 80°CUntargetedHPLC- MS/MS Shimadzu Prominence HPLC system with a column Phenomenex Luna C8 3 x 50 mm; AbSciex API-5000 triple quadrupole, ESISerum/ -80°CTargetedLC-MS/MS Waters HPLC system, Applied Biosystems API- 4000 MS/MS mass spectrometerSerum/ -20°CTargetedUPLC- MS/MS Waters Acquity UPLS system, Waters Triple QuadrupoleSerum/ -80°CTargeted | LC-MS/MS triple quadrupole Applera Amniotic Targeted Homocysteine API 3000, TurbolonSpray Ionisation Targeted NA UPLC- MS/MS Plasma/- Untargeted NA UPLC- MS/MS Plasma/- Untargeted NA HPLC- MS/MS Serum/ -80°C Targeted NA HPLC- MS/MS Serum/ -80°C Targeted 25(OH)D_2: Shimadzu Prominence HPLC system with a column Phenomenex Luna C8 3 x 50 mm; AbSciex API-5000 triple guadrupole, ESI Serum/ -20°C Targeted 25(OH)D_2; LC-MS/MS Serum/ -20°C Targeted 25(OH)D_2; 25(OH)D_3, HPLC- MS/MS Serum/ -20°C Targeted Methylmalonic Waters HPLC system, Applied Biosystems API-4000 MS/MS mass spectrometer Serum/ -80°C Targeted 25(OH)D_2; UPLC- MS/MS Serum/ -80°C Targeted 25(OH)D_2; 25(OH)D_2; Waters Acquity UPLS system, Serum/ -80°C Targeted 25(OH)D_2; Waters Triple Quadrupole Serum/ -80°C Targeted 25(OH)D_2; Waters Triple Quadrupol | Integraphy coupled to mass spectrometry LC-MS/MS Amniotic Targeted Homocysteine Unclear triple quadrupole Applera Amniotic Targeted NA NA UPLC-MS/MS Plasma/- Untargeted NA NA UPLC-MS/MS Plasma/- Untargeted NA NA HPLC-MS/MS Serum/-80°C Targeted 25(OH)D2; 6.3%*, Shimadzu Prominence HPLC-MS/MS Serum/-80°C Targeted 25(OH)D3; 6.6%*, HPLC-MS/MS Serum/-20°C Targeted 25(OH)D3; 6.5%*, 7.3%* (D3)/ AbSciex API-5000 triple quadrupole, ESI Serum/-20°C Targeted 25(OH)D3; 5.9%* (D3)/ LC-MS/MS Serum/-20°C Targeted Methylmalonic acid; <10%*; | Intermetry LC-MS/MS Anniotic fluid/-80°C Targeted Homocysteine Unclear 1Homocysteine LPLC-MS/MS Anniotic fluid/-80°C Targeted NA NA Hexacosategin digloceton UPLC-MS/MS Plasma/ - 80°C Untargeted NA NA Hexacosategin digloceton Orbitrap, ESI Plasma/ - 80°C Targeted NA NA Hexacosategin digloceton HPLC-MS/MS Serum/-80°C Targeted 25(OH)D2 6.3%6 ^a , 125.0H3/million 125.0H3/million Shimadzu Prominence HPLC-MS/MS Serum/-80°C Targeted 25(OH)D2 6.3%6 ^a , 125.0H3/million Phenomenex Luna CB 3 x So mm; AbSciex API-5000 triple 25(OH)D2 5.9% ^a (D2) 12.16m3/million AbSciex API-5000 triple guadrupole, ESI Serum/-20°C Targeted 25(OH)D2 8.2% ^a (D2) Name HPLC-MS/MS Serum/-20°C Targeted 25(OH)D2 5.9% ^a (D3)/ 10% ^a (D3)/ Waters HPLC system, Applied Biosystems API-4000 MS/MS mass spectrometer Serum/-80°C Targeted 25(OH)D2; 40% ^b ; Mame Waters Acquity UPLS system, Applied Biosystems API-4000 MS/MS mass spectrometer Serum/-80°C Targeted 25(OH)D2; 66% ^b ; <5% ^b / Waters Acquity UPLS syst | atography coupled to mass spectrometry LC-MS/MS Armiotic fluid/-80°C Targeted fluid/-80°C Homocysteine Unclear (Homocysteine (Homocysteine) UPLC- MS/MS Armiotic fluid/-80°C Targeted 80°C Homocysteine Unclear (Homocysteine) UPLC- MS/MS Plasma/- 80°C Untargeted NA NA Hexacosate (Homocysteine) Hexacosate (Homocysteine) UPLC- MS/MS Plasma/- 80°C Untargeted NA NA Hexacosate (Homocysteine) Hexacosate (Homocysteine) HPLC- MS/MS Serum/-80°C Targeted 25(OH)D ₂ 25(OH)D ₃ 6.3%*, 6.6%* (D ₂); 0.5%* (D ₂)/ unclear (12.16mg/m1 # 8.09- 6.5%*, 122.0Hg/m2 HPLC- MS/MS Serum/-20°C Targeted 25(OH)D ₂ 25(OH)D ₃ 8.2%* (D ₂)/ 5.9%* (D ₂)/ unclear Na HPLC- MS/MS Serum/-20°C Targeted 25(OH)D ₂ 25(OH)D ₃ 8.2%* (D ₂)/ 5.9%* (D ₃)/ Unclear Na HPLC- MS/MS Serum/-20°C Targeted 25(OH)D ₂ 25(OH)D ₃ 8.2%* (D ₃)/ 5.9%* (D ₃)/ Unclear Na HPLC- MS/MS Serum/-80°C Targeted 25(OH)D ₂ 25(OH)D ₃ 8.2%* (D ₃)/ 5.9%* (D ₃)/ 100/1 None UPLC- MS/MS Serum/-80°C Targeted 25(OH)D ₂ 25(OH)D ₃ 0.57mg/m1 0.57mg/m1 0.57mg/m1 0.57mg/m1 0.57mg/m1 0.57mg/m1 0.57mg/m1 0.57mg/m1 0.57mg/m1 0.57 | atography coupled to mass spectrometry LC-MS/MS Anniotic fluid/-80°C Targeted Homocysteine Unclear [Homocysteline] 10.65 MP 1000, TurbolonSpray ionisation Anniotic fluid/-80°C Targeted NA NA Hexacosadefilic acid, diglyce8b8/gyso- phosphate/syso- syso- |

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|---|---|--|--|--|---|---|---|------------------------------------|
| Ong YL et al, 2016 | LC-MS/MS Applied Biosystems ThermoHypersil BDS C8 reverse-phase column | Plasma/ Unclear | Targeted | 25(OH)D _{2;} 25(OH)D ₃ | ≤10,3% ^{a,b} / <1,6ng/mL | inguding for | 0.12/ 0.87 | |
| Wang Y et al, 2016 | LC-MS Agilent HPLC system, Applied Biosystems Sciex API-4000 triple quadrupole mass spectrometer | Serum/ Unclear | Targeted | PFOA; long- chain PFCA | 0,83- 7,94% ^a ; 1,57- 24,7% ^b / 0,07- 0,45ng/mL ^e | PFDeA (OF 35 4 1,07-9,19), F 5 4 1,83; 95% CI 1,83; 95% CI 6 c m f 5 5 6 c s 5 5 7 c s 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 | | |
| Gong S et al, 2018 | LC-MS/MS Shimadzu UK Limited UPLC system, ACE Excel 2 C18- PFP LC-column; Thermo Fisher Scientific Exactive orbitrap mass spectrometer | Serum/ Unclear | Untargeted | NA | | oademine ^f ∩N diacety⊌ata mining, | | |
| Morillon A-C et al, 2018 | UPLC- MS/MS Waters Acquity UPLS system, Waters Synapt G2-S mass spectrometer | Urine/-80oC | Untargeted | NA | en | aniopen.bmj.cou e Algraining, and : | | |
| Others | | | | | | n/ on simila | | |
| van Eijsden M et al, 2008 | GC-FID Solid phase extraction SPE, Capillary GC | Plasma/ - 80ºC | Semi- targeted, Lipid extraction | Elaidic, linoleic, alfa-linolenic, eicosatetraenoic, EPA, DPA, DHA DGLA, AA, Adrenic, and Osbond acids | ≤2 - 22% ^b / Unclear | ↓ Eicosate (OR 1,5; 95% CI 1,07- 2,91), ↓DPA (OR: ,489,95% CI 1,06-2,9) | | |
| certain based cervonyl carr pencosenoic hydroxybutyra phosphocoline (3s)-3,4-Di-N- | and ^b inter-assay coefficients of on chromatographic peak and nitine and/or 1-alpha,25-dihyc acid or cyclohexyl acetate o ate or hydroxy-methylpropanoa e or ubiquinone-8; acetylleucil-li- hexanoyloxybutyl-1-phosphocol holine (16:1) or cervonyl c | mass: Phenylac lroxy-18-oxocho r octanoic acio e or methyl me eucil-norleucina ine or N-(3-r arnitine; prega | etylglutamine of lecalciferol; (1 d or methyl-he ethoxyacetate; l or oleoylglyce hydroxy-propyl) nediol-3-glucur | or formyl-N-acetyl-5 5Z)-tetracosenoic eptenoic acid or 4 lysophosphocoline rone phosphate or arachidonoyl ar | i-methroxykyn acid or 10, i-hydroxy-2-oc and phospho LPA(0:0/18:2(nine or N-r ,20-alpha-dihy | urenamine; leucydeucyl-norl 13-dimethyl-11-decosyne-10, tenal or DL-2-aninooctano coline (more thag 10 hits); j 9Z,12Z)) or 1-16g lysoPE or nethyl N-(2-hydeoxy-ethyl) droxy-5-beta-preanane-3-glu | eucine or sphingosine 1-pl 13-diol or trans-selachol ic acid or 3-amino-octar phosphocoline (more than phosphocoline(O-11:1(10 arachidonoyl amine or | hosp leic loic 20 E)/2 |

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 19 of 56 BMJ Open (4OH,8Z,t18:1) sphingosine or 15-methyl-15-prostaglandin D2 or 15-R-prostaglandin E2 methylester. *Values for all statices female babies. AUC: area under the receiver operating characteristic curve: ¹H-NMR: hydrogen nuclear magnetic resonance: NOESY: nuclear Overhauser effect spectroscopy: GC-MS: gas

AUC: area under the receiver operating characteristic curve; ¹H-NMR: hydrogen nuclear magnetic resonance; NOESY: nuclear magnetic resonace; NOESY: nuclear magnetic resonance; NOESY: nuclear chromatography coupled to mass spectrometry; SPME: solid phase micro extraction; LC-MS: liquid chromatography coupled to mass spectrometry; UPLC: ultra-performance liquid chromatography; ESI: Electrospray ionisation; FID: flame ionisation detection; PFOA: perfluorooctanoic acid; PFCA: perfluorocarboxylic acid; PFDeA: perfluorodecanoic acid; PFUnDA: perfluoroundecanoic acid; EPA: eicoisapentaenoic acid; DPA: docosapentaenoic acid; DHA: docosahexa acid; DGLA: dihomo-gama-linolenic acid; AA: just 2019. Downloaded from http://bmjopen.bmj.com/ on June 13, 2025 at Agence Bibliographique nseignement Superieur (ABES) . es related to text and data mining, Al training, and similar technologies. arachidonic acid; OR: odds ratio; CI: confidence interval; NA: not applicable.

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Analysis of identified metabolites

The identified compounds refer to eleven HMDB chemical classes. Fatty acids
[18,28,39] comprised the most prevalent chemical class, followed by amino acids
[18,33] and phosphosphingolipids [17] (Table 3).

A total of 5,974 women were assessed for vitamin D status. Results were presented as total vitamin D, [32,35,37,40] although vitamin D₂ D₃ or 3-epi-25(OH)D₃ [35] metabolites were measured. Results were stratified according to season of maternal sampling or latitude. Either <15ng/mL (<37.5nmol/L) [40] or <20ng/mL (<50nmol/L) [32,35,37] levels characterized vitamin D deficiency, but were statistically different in SGA pregnancies only in the 1st trimester. [32] Horgan et al found a metabolite that could represent a vitamin D derivative, but it was only predictive in combination with 18 other compounds; this model had an area under the curve (AUC) of 0.90 (optimal odds ratio (OR), 44; 95%CI 9-214). [17]

The second most frequent targeted metabolite was homocysteine, [33,34] although levels were only differentiated between normal and SGA pregnancies when measured in 2nd trimester amniotic fluid, with a multiple linear regression model r^2 =0.012 and p=0.029. [33] Comparatively, the only common metabolite in 2nd trimester maternal hair was margarate, with conflicting results since it was found to be either increased (AUC 0.72, 95%CI 0.58-0.86) [28] or decreased. [18] The N1,N12-diacetylspermine and the perfluorocarboxylic acids were associated to female SGA babies, not males. The former presented a 5-fold decreased risk of SGA across quintiles. The perfluorodecanoic and perfluoroundecanoic acids presented OR of 3.14 (95%CI 1.07-9.19) and 1.83 (95%CI 1.01-3.32). [36] Tyrosine, an essential amino acid for infants, was part of the predictive model of maternal hair, combining 5 metabolites with an AUC of 0.998 (95%CI 0.992-1.0) [18]. However,

tyrosine did not predict SGA when urine samples were studied. [38] Methylmalonic acid, [34] acetate, formate, or trimethylamine, [38] did not differentiate SGA when compared to uncomplicated pregnancies (p>0.05). for occurrence of the occurren

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Table 3. Predictive metabolites summarized according to their chemical class, subclass, and biological process

| Predictive metabolites | Chemical class | Chemical subclass | Metabolicapatoway |
|--|--|---------------------------------------|--|
| Margarate | Fatty acyls | Fatty acids and conjugates | Lipid trans |
| Pentadecanoic acid | Fatty acyls | Fatty acids and conjugates | Lipid transport metabolism, peroxidation; fatty acid metabolism me |
| Myristic acid | Fatty acyls | Fatty acids and conjugates | Lipid trans |
| Eicosatetraenoic acid | Fatty acyls | Fatty acids and conjugates | Lipid transport metabolism, peroxidation; lipid metabolis |
| Docosapentaenoic acid | Fatty acyls | Fatty acids and conjugates | pathway 꽃은걸 Lipid transguttend metabolism, fatty acid metabolism, alpha linologe호흡cid and linoleic acid metabolisms |
| Tyrosine ^a | Carboxylic acids and derivatives | Amino acids, peptides, and analogues | Catechola in the biosynthesis; phenylalanine and tyrosine metabolism; and rotation and tyrosine synthesis; transcription an translation; and translation; and the biosynthesis; transcription and translation; and the biosynthesis; transcription and translation; and the biosynthesis; transcription and translation; and the biosynthesis; transcription; and the biosynthesis; and the biosynthesis; transcription; and the biosynthesis; and the biosynt |
| Homocysteine | Carboxylic acids and derivatives | Amino-acids, peptides, and analogues | Glycine and set ine metabolism; methionine metabolism |
| Hexacosanedioic acid | Carboxylic acids and derivatives | Dicarboxylic acid and derivatives | Fatty acid biosonthesis |
| Sphinganine 1-phosphate | Sphingolipids | Phosphosphingolipids | Sphingoliped signalling pathway, nneuroactive ligand- receptor interaction |
| Sphingosine 1-phosphate | Sphingolipids | Phosphosphingolipids / | Lipid meta |
| PFDeA | Alkyl halides | Alkyl fluorides | Not reported ^b |
| PFUnDA | Alkyl halides | Alkyl fluorides | Not reported b |
| 25,OH,Vitamin D | Steroids and steroids derivatives | Vitamin D and derivatives | Lipid metagolisin pathway |
| Diglyceride | Glycerolipids | Diradylglycerols | Adipocytolene gignaling pathway |
| Lactate | Hydroxy acids and derivatives | Alpha hydroxy acids and derivatives | Gluconeogenesis, glycogenosis types IB and IC, pyruva metabolism, trasephosphate isomerase |
| N1,N12-diacetylspermine | Carboximidic acids and derivatives | Carboximidic acids | hn 1 |
| Lyso-phosphocholine | Glycerophospholipids | Glycerophosphocholines | Not reported ^b Not |
| 2-methyloctadecanate | Saturated hydrocarbons | Alkanes | Not report ab S |
| Levulinate | Keto acids and derivatives | Gamma-keto acids and derivatives | Not reported b |
| ^a Essential amino acid for infa | ants. ⁰ No human metabolic pathways re | ported at KEGG. PFDeA: perfluorodecan | oic acid; PFUnDA perfluoroundecanoic acid. |

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1 Risk of bias and Applicability Concerns

Figure 2 shows synthesized data for all included studies. See Supplementary
Material 3 for individual QUADAS-2 data.

Regarding the risk of bias, all cohort studies conducted a consecutive participant inclusion. [28,33-37,39] Nested case-controls matched cases and controls randomly [33-35,41] or according to maternal and infant characteristics. [17,18,38,42] One study [41] failed to mention matching procedures ('Patient Selection' domain). Researchers were not blinded to SGA status when interpreting metabolomics results, [17,18,28,32,35–41] and thresholds of targeted metabolites were not pre-specified [31,33,36,38,39] ('Index Test' domain). Conversely, SGA identification was not influenced by the metabolomics test, although it was unclear when laboratory experiments were performed in some studies. [18,28,31,33,34,41] Birthweight charts were adequate, except for two studies. The first did not report which centile was chosen, [18] and the second used a centile designed for a different population [33] ('Reference Test' domain). Two studies were ranked as 'high risk' because not all participants were included in the analysis [31,37] ('Flow and Timing' domain).

The QUADAS-2 tool also highlights the importance of how the findings of the included studies are suitable to the review question. In the Patient Selection domain, it was ranked as 'high applicability concerns' when infants born between the 4th and the 10th centile, but with normal abdominal circumference growth velocity, were not included in final analysis. [41] It was 'unclear' when the gestational age of maternal assessment was not standardized, [34] or was inferred by hair segment length; [28] or when few metabolites from untargeted studies were chosen for interpretation [41]

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1 ('Index Test' domain). Finally, it was 'high' when the birthweight charts applied did
2 not correspond to the study population [18,33] ('Reference Standard' domain).

4 Meta-analysis

From the 15 included studies, only three were designed for prediction purposes [17,18,42] and provided the AUC. The remaining reports described statistical differences of metabolites between SGA pregnancies and controls. [28,31–41] Accuracy measures were extracted when available (Table 2). However, due to marked heterogeneity (Tables 1 and 2) of gestational age at sampling, type of samples used, type of birthweight chart chosen, thresholds for vitamin D deficiency, metabolomics approach, and identified compounds, a meta-analysis could not be performed.

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14 DISCUSSION

15 Main findings

In this first systematic review of metabolomics and adverse pregnancy endpoints, we presented techniques and metabolites, which were studied for the prediction of SGA. Any effect on birthweight has important implications for perinatal research, since it is related to short and long-term outcomes, [43-46] and in different generations. [47,48] Intrauterine environment influences fetal growth through epigenetic processes: altered gene expression potentially leads to distinct phenotypes. [49] Metabolomics is the most adequate approach to study this outcome, since it is most directly related to phenotype. [50]

Interpretation of metabolomics findings in pregnancy can be challenging.
 Firstly, maternal metabolites concentrations are influenced by placental transfer to

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and from the fetus. The 'mirror effect', seen for maternal plasma and venous cord blood metabolites at birth, [51] cannot be ruled out when only maternal specimens are studied. Secondly, maternal exposure to distinct compounds may affect metabolite levels. Statistically significant differences between SGA infants and controls may not express the totality of underlying pathological pathways and have no clinical meaning. Finally, it is unclear when the processes leading to SGA are initiated. The disruption in maternal metabolism can theoretically occur at any time. In general the lower the gestational age at which the condition is suspected, the more severe the phenotype will be at birth. [52,53] Thus, the description of clinical data in translational studies must deal with all these confounding factors.

Gestational age at sampling is probably the most important parameter for prediction purposes. With timely prediction, women could be referred to specialized care, have increased surveillance, and this in turn may lead to a reduction in perinatal mortality. There are temporal changes in the maternal metabolome during pregnancy: [28,54–57] therefore, it is reasonable to expect distinctive metabolites at different stages of pregnancy, as reported here. Unfortunately, a wide or unclear definition of gestational age of sampling [34,36,38,40] render a more precise interpretation impossible, and may limit the clinical application of these results.

In contrast, gestational age at birth and birthweight centile seem to be the hallmarks of severity and prognosis of growth restriction. [6,58] Indeed, term and preterm SGA babies show distinct clinical phenotypes, and there are concerns that some babies <10th centile of birthweight are constitutionally small infants. [59–61] If only term deliveries are evaluated, the most severe cases of growth restriction may be potentially missed. Moreover, when term and preterm births are analyzed together, or when lower cutoffs are not specified (e.g. $\leq 3^{rd}$ or $\leq 5^{th}$ centile), the lack of

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predictive metabolites might mean that they are distinct conditions. Thus, we hypothesize that the predictive performance of metabolomics may be improved if data is analyzed by gestational age at delivery, and by different cutoffs of birthweight centiles.

Evidence suggests that tobacco smoke has an impact on birthweight, [62-64] although it is uncertain how and when fetal growth is impaired. It is possibly related to oxidative stress, [65] and both maternal and fetal metabolism may be disturbed at delivery. [66,67] Studies that were included did not investigate cigarette-related chemicals or quantify exposure to tobacco smoke. Therefore, no relationship between SGA and tobacco was found. Hence, we suggest that tobacco interferes with ongoing metabolic pathological processes, or its disturbance is related to additional metabolic pathways other than the one examined by the included studies.

14 Subgroup and metabolite findings

No reports have explored data on any maternal chronic condition, suspicion of SGA
in pregnancy, or number of fetuses. The lack of clear statements about participant
selection have hindered data interpretation and precluded these analyses.

The majority of included studies performed a targeted approach, i.e. a hypothesis-testing evaluation, [16,50] driven by epidemiological or experimental data regarding SGA newborns. None of the targeted metabolites [31–40] were in common with those found by 'hypothesis-generating' metabolic profiling [17,18,28,41,42] investigations. This reinforces the suggestion that various maternal metabolic pathways may be triggered by the SGA condition, and be detected by different biological samples. However, since blood is a very complex sample and GC-MS only

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evaluates volatile molecules, [50] therefore our findings may be biased by studymethodologies.

3 Untargeted studies, as expected, have characterized several metabolites 4 that may be validated in future investigations. Nine lipids and fatty acid metabolites, 5 [17,18,28,39] two amino acids, [18,33] and a steroid [17,32] have been identified as 6 potential biomarkers of SGA.

All lipid-related metabolites identified are intermediates for energy storage and breakdown. Most metabolites were found in maternal blood [17] or hair of the SGA group. [18,28] Blood levels of saturated and monounsaturated non-esterified fatty acids apparently remain stable throughout pregnancy, while long chain polyunsaturated fatty acid (DHA and EPA, for example) measurements seem to show ethnicity-related changes. [57] Experimental data shows the importance of hypoxia and oxidative stress to placental function and ultimately, to birthweight. [68,69] Findings from included studies may represent a dysregulation of lipid pathways at the placental level, but an association with maternal background is unclear. Therefore, we hypothesize that disorders of lipid metabolism may be the 'metabolic snapshot' of defective deep placentation, [70] and might reflect maternal efforts to respond to impaired fetal growth.

Recommendations on the assessment of vitamin D and cutoffs to define vitamin D deficiency in pregnancy are controversial. [71] However, vitamin D supplementation decreases SGA risk. [72] In early pregnancy, vitamin D status has been related to SGA, [73,74] which is in accordance with this review, despite the inconsistent findings. [75] There is evidence that trophoblasts actively produce and secrete vitamin D metabolites, [76] but it is not clear how they mediate fetal growth impairment. Altered hepatic gene expression and liver function in vitamin D deficient

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female rats, [77] and single nucleotide polymorphisms [78] in vitamin D receptor
gene have been suggested as mechanisms to be explored by a multidimensional
omics approach.

Finally, homocysteine is an intermediate metabolite of the folate cycle. It is indirectly involved with DNA methylation and is a marker of folate deficiency. [79] Maternal levels rarely reach hyperhomocysteinemia limits, [80] but folate depletion [81–83] and homocysteine itself[80] are thought to be associated with a higher SGA risk. In this review, homocysteine was only statistically different in SGA pregnancies when measured in amniotic fluid, [33] although within the normal ranges proposed for 17-21 weeks. [84] Since amniocentesis is generally performed in women at higher obstetrical risk, future studies should investigate whether homocysteine in amniotic fluid represents a confounding factor or a new biomarker. [85]

Meth

Methodological quality

Most studies were ranked as 'low risk' of bias or applicability to the review question.
However, the lack of clear descriptions of laboratory experiments, including sample
preparation and storage, and blinding of the researchers to the case/control status,
are major pitfalls of the included studies.

20 Strengths and limitations

To our knowledge, this is the first systematic review of metabolomics and an adverse
pregnancy outcome (SGA). We presented possible biomarkers of SGA
pathophysiology, metabolites implicated in lipid transport and metabolic pathways,
as well as gluconeogenesis.

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However, this analysis has some limitations. First, included studies showed heterogeneity, which is fundamental in systematic reviews. Indeed, there was a wide variety of participant characteristics and methods used, and not all authors provided a detailed description of methods employed. Although the Metabolomics Standard Initiative was released in 2007, [86] there is still poor adherence to guidelines. [87,88] Clear reporting [15,87,88] and data sharing in repositories are crucial steps in identifying features of interest, specifically possible biomarkers to be validated in the clinical studies. [15] Secondly, we could not perform a meta-analysis of the extracted data, impacting the translational potential of metabolomics.

Thirdly, we considered that birthweight was a surrogate measure of intrauterine development. SGA and FGR are not interchangeable concepts. However, SGA has been used as a surrogate for FGR in many clinical studies due to difficulties in defining optimal intrauterine growth: (i) FGR diagnosis relies mostly on ultrasound measurements of fetal biometry, [3,89] which in turn is subject to systematic errors; [90] (ii) intrauterine development is adaptive, rather than uniform [91] or only genetically driven; [49] (iii) growth impairment at birth better identifies adverse neonatal outcomes than during pregnancy. [58] It is recognized that changes in obstetric care occur when growth restriction is suspected, and neonatal outcomes are improved. [21,22] Thus, an accurate prediction of SGA during pregnancy will be a turning point in modern obstetrics.

22 CONCLUSIONS AND IMPLICATIONS FOR PRACTICE

Using the available clinical tools, efforts to predict SGA remain disappointing. Since
 SGA is a heterogeneous condition, it benefits from metabolomics. This novel area of
 research allows analysis of numerous types of biological fluids and detects

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thousands of metabolites in complex samples. [15,16,25] However, findings of this systematic review must be interpreted with caution. The type of samples used may have influenced LC-MS (2nd trimester maternal blood) and GC-MS (2nd trimester maternal hair) findings in individual studies. Furthermore, the prediction of SGA in the context of maternal disorders, suspected FGR and twin pregnancies is an open field for future metabolomics studies, and environmental exposure investigation as well.

Surprisingly, none of the studies used $\leq 3^{rd}$ centile of birthweight as a cutoff or analyzed preterm deliveries and hypertensive syndromes. Considering our findings and the different phenotypic manifestations of SGA, we envision a better performance when (i) cutoffs other than the 10th centile are tested; (ii) data on gestational age at sampling and at birth are standardized; and (iii) other pregnancysyndromes are considered, especially hypertension. related Thus, future metabolomics results should advance in these critical points.

Finally, all detected biomarkers were related to lipid pathways and energy metabolism. We consider that research efforts to predict SGA should focus on compounds involved in these pathways, up to the 2nd trimester of pregnancy.

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1 AUTHORS CONTRIBUTIONS

DFBL and ACM have equally contributed to this report, and both are guarantors of this review. They elaborated the protocol, searched the literature, selected studies, extracted data, assessed risk of bias, and drafted the initial manuscript. RTS and EFMJ have participated in judging inclusion of studies, interpreting data, and revising the manuscript. FM have supported data extraction and have critically examined the clinical interpretation of results. ASK has discussed the quantitative data synthesis, and supervised the report writing. PNB, LCK, and JGC have supervised and approved all steps. All authors have read and agree with this submission.

11 ACKNOWLEDGEMENTS

We are grateful to (i) Shauna Barret, from the Brookfield Library, University College Cork, Ireland, for her support with the literature search; (ii) Ting-Li Han, from the Department of Obstetrics, The First Affiliated Hospital of Chongqing Medical University, China, for providing additional data for this systematic review; (iii) and Luis Felipe D'Orsi, from University of Campinas, for his support with methods' issues.

19 FUNDING

DFBL (process number 88881.134512/2016-01) and RTS (88881.134095/2016-01) have awarded scholarships from Brazilian Federal Agency for Support and Evaluation of Graduate Education (CAPES). ACM was granted a scholarship from Science Foundation Ireland, for her doctoral thesis. PRETERM-SAMBA has granted sponsor from Brazilian National Research Council (CNPq) (Award 401636/2013-5) and from the Bill and Melinda Gates Foundation (grant OPP1107597), corresponding

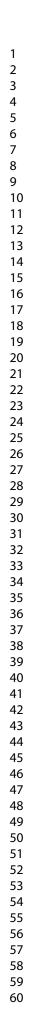
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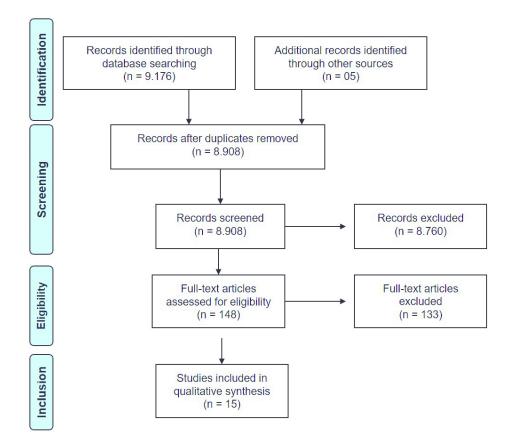
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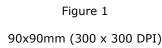
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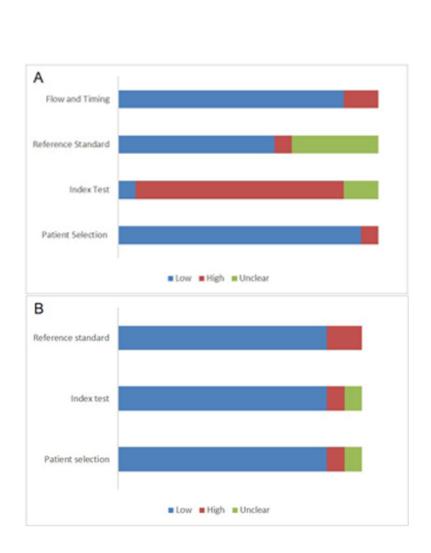
2 number 05/2013. This research received no specific grant from commercial or not-3 for-profit sectors. Our sponsors have not intervened in authors' decision to write the 4 systematic review protocol or to submit this paper. 5 6 **COMPETING INTERESTS** 7 None to declare. 8 9 **PROVENANCE AND PEER REVIEW** 0 Not commissioned; externally peer reviewed. 1 2 **Figure captions** 3 Figure 1. PRISMA flowchart of study identification, screening and selection. From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred 4 5 Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097. For more 6 7 information, visit <u>www.prisma-statement.org</u>. 8 Figure 2. Assessment of risk of bias (A) and applicability concerns (B) of individual 9 20 studies. 21 2 Supplementary material description 23 Supplementary material 1 – Detailed literature search strategy. Supplementary material 2 - List of excluded studies and reasons. 24 25 Supplementary material 3 - Individual QUADAS-2 data for all 15 included studies.







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Examining the predictive accuracy of metabolomics for small for gestational age babies: a systematic review

Debora F. B. Leite and Aude-Claire Morillon; Elias F. de Melo Junior; Renato Teixeira Souza; Fergus P McCarthy; Ali S. Khashan; Philip N. Baker; Louise C. Kenny; Jose G. Cecatti

Supplementary material 1 – Detailed literature search strategy.

| 1 | fetal growth retardation |
|----|--|
| 2 | fetal growth restriction |
| 3 | intrauterine growth restriction |
| 4 | intrauterine growth retardation |
| 5 | small for gestational age |
| 6 | #1 OR #2 OR #3 OR #4 OR #5 |
| 7 | metabolomic* |
| 8 | metabonomic* |
| 9 | metabolit* |
| 10 | HNMR |
| 11 | proton NMR |
| 12 | proton nuclear magnetic resonance |
| 13 | liquid chromatogra* |
| 14 | gas chromatogra* |
| 15 | UPLC |
| 16 | ultra-performance liquid chromatograph* |
| 17 | ultra performance liquid chromatograph* |
| 18 | #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 |
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| 24 | #19 OR #20 OR #21 or #22 OR #23 |
| 25 | screen* |
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| 7 8 9 | Kenny, José Guilherme Cecatti. | | | August 2019. Enseignem uses relatec |
| 10 11 12 13 | Supplementary material 2 – List o | f excluded studies and reaso | ns. | Dov |
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| Maekawa R et al, 2017 | Japan | Cross-sectional study. | |
| Mao D et al, 2010 | China | Cross-sectional study. | |
| Miranda J et al 2018 | Spain | Cross-sectional study. | |
| Powell et al, 2018 | Australia | SGA babies not suspected before birth were | |
| Spanou L. et al, 2017 | Greece | Cross-sectional study. | |
| Stein TP et al, 2008 | United States | Newborns with birth defects were included in the analysis. | |
| Tang R et al, 2013 | China | Cross-sectional study. | |
| Visentin S et al, 2017 | Italy | Maternal samples collected after clinical receptinition of FGR/SGA. | |
| Zhu Y et al, 2018 | China | Cross-sectional study. | |
| Zota AR et al, 2009 | United States | Cross-sectional study. The metabolomics tegenigue was not applied. | |
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 Examining the predictive accuracy of metabolomics for small for gestational age babies, a systematic review

 Debora F. B. Leite & Aude-Claire Morillon, Elias F. Melo Júnior, Renato T. Souza, Fergus P. McCarthy, Ali S. Khashan, Philip N. Baker, Louise C. Kenny, José Guilherme Cecatti.

 Supplementary material 3 - Individual QUADAS-2 data for all 15 included studies.

| | | | | Risko | of bias | Augu Eng | | |
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| | Patient s | selection | Inde | x test | Reference | e standard e gn a n 20 | Flow an | d timing |
| Studies | Was a consecutive or random sample of patients enrolled? | Did the study avoid inappropriate exclusions? | Were the index test results interpreted without knowledge of the results of the reference standard? | If a threshold was used, was it pre- specified? | Is the reference standard likely to correctly classify the target condition? | Constant of the | Did all patients receive the same reference standard? | Were all patients included in the analysis? |
| Grandone E et al, 2006 | Yes | Yes | Unclear | No | No | B. Chaear | Yes | Yes |
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| 6 | | | Applicability concerns | for | |
| 7 8 | | Patient selection | Index test | Ens | |
| 9 10 11 12 | Studies | Are there concerns that the included patients do not match the review question? | Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Are the defended | concerns that the target condition as by the reference standard does not match the review question? |
| 13 | Grandone E et al, 2006 | No | No | t Su tex | Yes |
| 14 | van Eijsden M et al, 2008 | No | No | peri l and | No |
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PRISMA 2009 Checklist

BMJ Open **IA 2009 Checklist** Examining the predictive accuracy of metabolomics for small for gestational age babies: a systematic review

Debora F. B. Leite & Aude-Claire Morillon, Elias F. Melo Júnior, Renato T. Souza, Fergus P. McCarthy, Ali S. Khashan, Philip N. Baker, gouge C. Kenny, José Guilherme Cecatti

| Section/topic | # | Checklist item | Reported on page # |
|------------------------------------|----|--|--------------------|
| TITLE | | ateen teen | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| ABSTRACT | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data souther study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations and implications of key findings; systematic review registration number. | 3-4 |
| INTRODUCTION | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 5 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants in prventions, comparisons, outcomes, and study design (PICOS). | 6 |
| METHODS | | ng, and and a second seco | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and if available, provide registration information including registration number. | 6 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 7-8 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with stady authors to identify additional studies) in the search and date last searched. | 6-7/ 9 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits use, such that it could be repeated. | 6-7 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 7-8 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplic te) and any processes for obtaining and confirming data from investigators. | 8 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 7-8 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specificatio ເຊັ້ of whether this was done at the study or outcome version and hove this internation is to be used in any data synthesis. | 8-9 |

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| IDRIS MET | PRISMA 2009 Checklist |

BMJ Open **IA 2009 Checklist** Examining the predictive accuracy of metabolomics for small for gestational age babies: a systematic review

| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 9 |
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| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including the asures of consistency (e.g., I ²) for each meta-analysis. | 9 |
| | | Page 1 of 2 | |
| Section/topic | # | Checklist item | Reported on page # |
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., public above bias, selective reporting within studies). | 8-9 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regionsion), if done, indicating which were pre-specified. | 7 |
| RESULTS | • | A B | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 9 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PLCOS, follow-up period) and provide the citations. | 9-13 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessme | 23-24 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot | 20-22 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measure of consistency. | 24 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 9; 23-24 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | NA |
| DISCUSSION | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 24-28 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., if complete retrieval of identified research, reporting bias). | 28-29 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implication for future research. | 29-30 |

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| 10 | systematic review. | _ 0 ÷ | • | |
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